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A DISEASE IN INFANTS RESEMBLING CHRONIC WERNICKE'S ENCEPHALOPATHY

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WERNICKE'S encephalopathy (hemorrhagic polioencephalitis superior) is a relatively uncommon disorder that has been described in adults who have been deprived of an adequate diet by alcoholism,[1-3] by war exigencies,[4, 5] or by gastrointestinal, febrile, or debilitating diseases.[6-10] These observations, together with experimental data,[11-19] suggest a nutritional basis for the disease,[20, 21] more specifically a thiamine deficiency.

The disease is characterized clinically by disturbances in consciousness, paralyses of the external ocular muscles, and ataxia, although in many cases this triad is incomplete.[22] Degenerative lesions associated with capillary changes and often with petechial hemorrhages are found principaliy in the periaqueductal gray matter of the midbrain, and the walls of the third and fourth ventricles.[2, 6]

The occurrence in children of a similar disease process has been reported from Japan[23-26] as "breast milk intoxication" since it occurred in infants who were breast fed without supplementary feeding. More recently the clinical aspects of similar cases have been reported from the Philippines.[27]

This paper will describe three cases of this disease in American children who came to autopsy.

CASE REPORTS

CASE 1.—J. L. A. (No. 6980) was a full-term, normally delivered white male infant. No jaundice was observed. He had been breast fed for nine days but was subsequently placed on an evaporated milk formula containing Dextri-Maltose No. 1. He did not take feedings well and would leave some of the formula or regurgitate part of it during the feeding or immediately afterward. When 6 weeks old he was started on orange juice, which he apparently took well but which produced a rash. Ascorbic acid tablets were substituted for the orange juice, and these were well tolerated. At the age of 2 months the baby was given cereals, but these were refused frequently. At the age of 5 months he could not hold his head up. A pediatrician diagnosed the condition as "muscular weakness" and prescribed vitamin B_1 and liver injections every other day, as well as wheat germ oil by mouth. With this treatment there seemed to be some improvement in that the baby apparently tolerated the feed-

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ings better, but his nutrition and development continued below average. At the age of 7 months he was able to hold his head up but could not sit up. He was considered to be mentally deficient. His food intake remained below normal and his general nutritional status poor until his death at the age of 12 months. During the last three months of his life he was constipated and ran a low-grade fever. There are two older siblings who are apparently well.

When the infant was admitted to the hospital at the age of 12 months, a physical examination showed an apathetic, puny, acidotic, dehydrated white baby who appeared chronically ill and was obviously mentally retarded. The head was of normal size for his age. The pupillary reaction to light was questionable. The extraocular movements were inconsistent, and there was a bilateral internal strabismus. The palate moved bilaterally and the gag reflex was present. The fundi could not be observed. There was spasticity and weakness of all four extremities, more marked in the legs. The child occasionally performed jerky, purposeless movements of the extremities. There was a patellar clonus bilaterally, but the ankle jerks were only feebly elicited. The patient was unable to sit up and reacted poorly. The laboratory findings were negative except for a low CO_2 combining power of the blood on admission and a throat culture positive for pneumococcus, type III. During the hospital stay the baby failed to improve in spite of feeding by gavage and multiple vitamin therapy. He remained drowsy and apathetic and continued to run a low-grade fever. Two weeks after admission the temperature rose to 101° F., and he developed severe respiratory distress from which he did not recover.

Necropsy.—The body weighed 5,600 grams and measured 69 cm. in length. The circumference of the head measured 41 cm., of the chest 38 cm., and of the abdomen 40 cm. The body was underdeveloped and poorly nourished.

There was a small myoma 6 mm. in diameter within the substance of the posterior leaflet of the mitral valve. The lungs were the site of a diffuse bilateral aspiration pneumonitis. The liver showed mild fatty degeneration. There were no other significant changes in the general organs.

The sutures of the skull were fused and relatively well calcified. The anterior fontanel was open. The brain weighed 740 grams prior to fixation. The cerebral hemispheres were approximately symmetrical. The gyral pattern was complex, but within normal limits. The brain tissue was somewhat firmer than average. The cerebellum and brain stem were externally negative. The leptomeninges were moderately congested and translucent. The arteries at the base of the brain were normal in distribution and caliber and had delicate walls.

On sectioning the cerebrum, the lateral and the third ventricles were found to be slightly enlarged. There were symmetrical areas of pink-gray discoloration in the ventral halves of the lateral walls of the third ventricle posteriorly, beginning approximately 7 to 8 mm. behind the corpora mammillaria. On the right, this band of discoloration measured approximately 3 mm. in its greatest width, and on the left, approximately 4 mm. Between the ventricular surface and the inner margin of the area of discoloration there was a narrow ribbon of white tissue. The ventral aspect of each area of discoloration was light brown or reddish in color and was slightly spongy. These two fingerlike areas of abnormal tissue were continuous with an abnormal zone about the aqueduct of Sylvius (Fig. 1). Here the dorsal part of each anterior corpus quadrigeminum had a retracted, finely spongy, grayish-pink or yellow appearance and was softer than the surrounding tissue. This was continuous with a periaqueductal zone of similar character extending asymmetrically toward the left. This entire midbrain lesion measured approximately 1.5 cm. from side to side in the colliculi and

0.9 cm. about the aqueduct of Sylvius. There was a band of firmer white tissue immediately about the lumen of the aqueduct in the region of the lesion, similar to that about the third ventricle. The abnormal zone extended caudally into the posterior corpora quadrigemina, which were quite soft, dull reddish brown, finely spongy, and softer than the cephalic portion of the lesion. The right substantia nigra in its caudal portion was slightly sunken, soft and similarly discolored, whereas the left showed similar changes in its discoloration in the subependymal region of the cephalic portion of the medulla, which extended almost to the midline. They were not discernible below this until the region of the decussation of the lemnisci was reached where a roughly symmetrical U-shaped zone of discoloration, with its base passing through the region of the central canal dorsally and its arms passing laterally through the middle of each one-half of the medulla were seen. That on the left almost reached the pyramids. This tissue was slightly

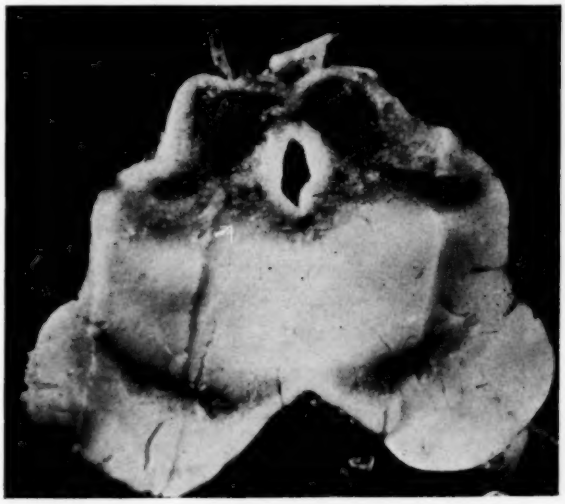

Fig. 1.—Case 1. Midbrain. Symmetrical lesions in the periaqueductal gray matter, the superior colliculi, and the substantia nigra. Note preservation of the subependymal tissues. (×6, reduced ¼.)

medial one-half. The upper portion of the pons showed a similar discoloration of the medial aspect of the floor of the fourth ventricle continuous with the periaqueductal lesions, extending caudally to the facial colliculi. At the level of the facial colliculi there were zones of discoloration in the ventrolateral angles of the subependymal region of the fourth ventricle, which was greater on the right than on the left and measured approximately 2 by ½ cm. These extended in the caudal direction and were continuous with narrow, less clearly visible bands of sunken, dull reddish brown, and firm. At the level of the decussation of the pyramids the area of discoloration was limited to the region of the central canal. Section of the cerebellum revealed no abnormalities of the parenchyma. The spinal cord appeared normal except for leptomeningeal congestion.

Microscopic examination confirmed the presence of lesions in the areas described with involvement of the posterior portion of the wall of the third ventricle, the red nuclei, the superior colliculi, the substantia nigra, the peri-

aqueductal gray matter (Fig. 2), and the tegmentum of the pons and medulla, so that the nuclei of the third, fourth, fifth, sixth, seventh, eighth, tenth, and twelfth nerves were affected. There were no lesions in the cerebellum or spinal cord. These lesions consisted of areas of rarefaction and loss of architecture within which neurons had partially or completely disappeared. The persistence of neurons, usually normal, sometimes shrunken, in severely altered zones, was a striking feature. There was a marked loss of myelin sheaths in these areas, with a significantly lesser degree of axon loss. The tissue within the rarefied zones consisted of a meshwork of fine glial fibers. There was no significant increase in the number or size of the astrocytes, no apparent increase in microglia, no phagocyte formation and the oligodendroglia were considered approximately normal in number and appearance. Dilated, congested, somewhat tortuous capillaries were seen, apparently in much larger numbers than normal, due partly to condensation. Many of these showed an increase in the number of endothelial cells in their walls and a slight increase in collagen. Many of the vessels were congested, and a slight extravasation of red cells was present in areas. There were no deposits of blood pigment. A band of subependymal tissue was characteristically preserved between the devastated areas and the ependyma.

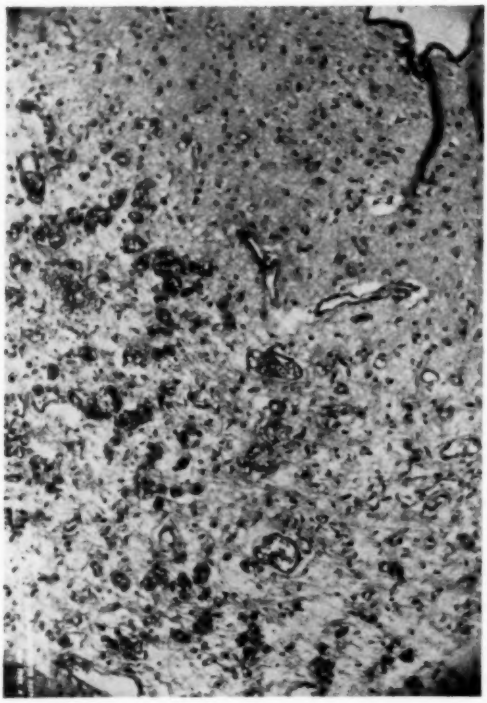

Fig. 2.—Case 1. Midbrain. Periaqueductal gray matter with wall of aqueduct in right upper corner. Note the rarefaction of the tissue, the vascular proliferation, the congestion, the fresh small hemorrhages, and the normal-appearing subependymal area. (H & E stain; ×150; reduced ⅓.)

Summary.—A male infant died at 12 months of age of a slowly progres-

sive disorder insidious in onset, characterized by a failure of normal growth and development, spasticity, motor weakness, mental deficiency, bilateral strabismus, jerky purposeless movements of the extremities, and, terminally, a low-grade fever. At autopsy, focal bilaterally symmetrical chronic lesions were found in the walls of the third ventricle, about the aqueduct, and in the floor of the fourth ventricle, characterized by partial neuron loss, marked myelin destruction, a lesser loss of axons, marked rarefaction of the tissues, minimal astrocytic response, a marked increase in the number, tortuosity, size, and cellularity of congested capillaries visible in the area, and a rare small hemorrhage.

CASE 2.—This 21-month-old male infant was the second child of parents who were first cousins. The first child of this marriage is described in Case 3 of this report. The mother stated that she was quite well throughout pregnancy. Birth was at term following a four-hour normal labor and spontaneous delivery. Birth weight was 7 pounds 4 ounces, and vital signs were normal. The child was on formula feeding from the beginning. During the first months of life he had a two-week bout of diarrhea, and at the same time there was a skin eruption which was treated with gentian violet by the family doctor. In spite of the parents' claim that the child developed normally thereafter, it was found upon examination at 17 months of age that he still could not stand or walk without aid. A neurological examination disclosed mild trunkal ataxia, the infant standing, when supported, on a wide base. Generalized muscular weakness, especially of the trunk, was present. There was a questionable pallor of the temporal portions of the optic discs, and bizarre movements of the eyes were noted. There was no evidence of disturbance of any of the other cranial nerves. The child had a slight dorsolumbar kyphosis. He died suddenly without any evidence of progression of the disease process. Specific nutritional data are not available, although the parents are intelligent, educated, and not impoverished, and there is reason to believe an adequate diet was offered.

At autopsy, the heart revealed a slight ventricular hypertrophy. The viscera were congested and the lungs were somewhat edematous. The follicles of the spleen were hyperplastic. The adrenal medulla was large in size.

The cerebrum was long in contrast to its breadth. The leptomeningeal vessels were mildly congested. The cerebral white matter was proportionately smaller than that present in the adult. The cerebrum was otherwise normal. The cerbellum showed no changes. The corpora Luysii were light brown in color, spongy, and retracted from the cut surface. Roughly lunate areas of light brown discoloration approximately 4 mm. in width and 2 mm. dorsoventrally were noted in the dorsolateral portions of the posterior corpora quadrigemina. Similar rounded lesions, approximately 2 mm. in diameter, were noted in the ventrolateral aspects of the tegmentum of the rostral portion of the pons. Roughly triangular, sunken, slightly brown, spongy zones of degeneration, approximately 3 to 4 mm. in width and 2 mm. dorsoventrally, were present in the floor of the fourth ventricle, being most conspicuous at the lateral angles, at the level of the lower pons. The regions of the fourth and sixth nerve nuclei were faintly brown in color. Oval areas of similar discoloration, approximately 2 to 3 by 2 by 1 mm. in size, were located in symmetrical positions, at the junction of the tegmentum and basilar portions of the pons, approximately 3 to 4 mm. from the midline. At the junction of the pons and medulla, the subependymal band of degeneration extended in a more continuous line across the entire floor of the fourth ventricle, becoming broader at either end and involving the region of the twelfth, tenth, and eighth nerve nuclei (Fig. 3).

Microscopically, lesions were observed in the optic chiasm and tracts, the corpora Luysii, the substantia nigra, the corpora quadrigemina, the superior cerebellar peduncles, the nuclei of the third and fourth cranial nerves, the motor and sensory nuclei of the fifth nerves, the inferior olives, the vestibular nuclei, the dorsal nuclei of the tenth nerves, the nuclei of the twelfth nerves, the reticular zone of the medulla, and the ventral gray horns of the lower medulla. The cerebrum showed only focal areas of congestion, and the mammillary bodies were normal.

Fig. 3.—Case 2. Medulla. A continuous band of lesions in the floor of the fourth ventricle and others in the reticular formation. Note preservation of the subependymal tissues. (×2.)

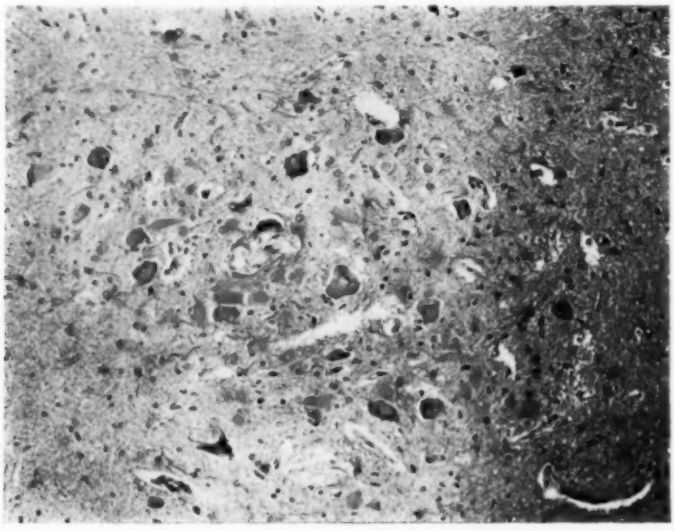

Fig. 4.—Case 2. Medulla. Acute chromatolysis of neurons in inferior olive. (H & E stain; ×150; reduced 1/5.)

The lesions were characterized by rarefaction and a partial loss of neurons. Within the rarefied areas a few neurons persisted, and most of these appeared normal. In the inferior olives, the reticular formation of the upper medulla, and the ventral gray matter of the caudal medulla, acute neuronal changes were indicated by a marked swelling, pallor, loss of Nissl substance, and eccentricity of nuclei (Fig. 4). Demyelinization (Fig. 5) was marked, and there was a slight to moderate loss of axons (Fig. 6). A moderate microglial proliferation was observed in some lesions, these cells assuming a rod-cell form. There was a slight astrocytosis, chiefly marginal, the cells being small and shrunken in the older lesions and large and swollen

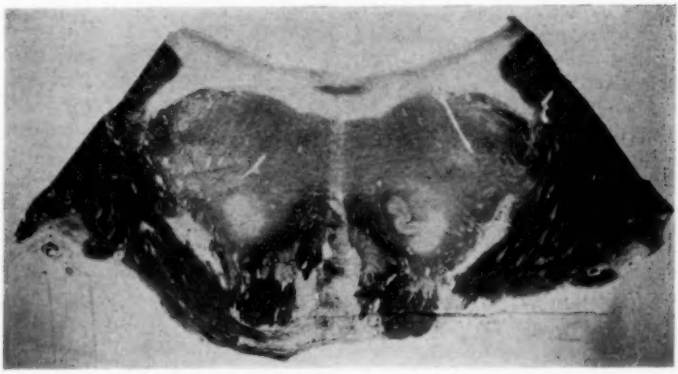

Fig. 5.—Case 2. Junction of pons and medulla. A continuous band of demyelinization in the floor of the fourth ventricle, indicating a series of coalescent lesions. Similar lesions are present in the reticular formation and the inferior olives. (Mahon stain; ×6; reduced ⅕.)

Fig. 6.—Case 2. Pons. Note relative preservation of axons within a lesion in the tegmentum in which the myelin sheaths were all degenerated. (Bodian stain; ×150; reduced ⅕.)

in those with the acute neuronal changes. The capillaries showed an increase in connective tissue fibers, and mural cells appeared to be increased in number. No hemorrhages were noted, though mild congestion was present in some areas. There were no deposits of blood pigment. A lesion was present in the optic chiasm, occupying much of the central portion of this structure. This lesion was characterized by pallor, rarefaction, a marked loss of myelin, a slight loss of axons, a mild increase in astrocytes, which were essentially piloid in form, an equivalent increase in glial fibers, and an apparent increase in the number of other glial cells, presumably by condensation of tissue.

Summary.—No "obvious defect" was noted in this male child by his parents or family physician until he was 17 months of age, although he still could not stand or walk unaided at that time. It was then noted that there was generalized motor weakness, mild trunkal ataxia, and bizarre movements of the eyes. The patient died unexpectedly at 21 months of age. Autopsy revealed the presence of chronic lesions in the floor of the fourth ventricle, the periaqueductal region, the corpora Luysii, and the optic tracts. These areas were rarefied and showed a partial loss of neurons, with some of those remaining showing acute changes, a marked demyelinization, a lesser axon loss, a moderate microglial proliferation, a slight astrocytosis, and a marked apparent increase in the capillaries, which were congested, tortuous, of increased cellularity, and somewhat fibrotic.

CASE 3.—E. W., a 4-year-old female child, was the older sister of the infant described in Case 2. The mother had had no previous pregnancies. She had suffered a "virus infection" in the fifth month of pregnancy. She also described this as a "severe cold" which lasted for over a week. The child was born at term by a normal spontaneous delivery following seven hours of labor. She weighed 6 pounds 8 ounces at birth, appeared "normal," and was placed on a formula at once. Appetite had been very poor since birth, though the diet offered had been adequate and included vitamin supplements. The patient suffered from frequent upper respiratory infections during the early months. She was vaccinated when 6 months old, with a severe local and generalized febrile reaction. At 8 months of age, a marked internal strabismus of the right eye was noted, which is said to have disappeared in less than two months. At 10 to 12 months of age, a series of frequent episodes of vomiting without diarrhea and with even more marked anorexia resulted in hospitalization for about two weeks, from which the patient was discharged improved. Her growth and development, which until this time appeared to be normal, now became progressively retarded. When 2 years old, the patient was again hospitalized for study. Nutrition seemed good, although body development, as indicated by weight and length, was far below average. The mental status was slightly below average and the skull was small. Prominent epicanthic folds but no other stigmas of Mongolism were observed. A slight right internal strabismus, an intermittent nystagmus, a marked generalized ataxia, and a generalized tremor of head, trunk, and extremities, increased by intention and absent while sleeping, were observed. The musculature was generally weak and hypotonic, with decreased but no abnormal reflexes. Sensation was normal. During the next year, the child progressively deteriorated with marked weakness and lack of normal activity. An examination at 3 years of age disclosed an internal strabismus, flaccid extremities which did move on painful stimuli, and normal deep reflexes. A pneumoencephalogram revealed normal or slightly dilated ventricles. There was a transient significant improvement in weight and strength in the next six months with a return of

the marked weakness thereafter. Death occurred presumably as a result of a bronchopneumonia, although autopsy limitations precluded confirmation.

Gross examination of the brain revealed evidence of swelling of the cerebrum, as indicated by compression of the ventricles and of the sulci. There were two vertical linear areas of gray discoloration on the anterodorsal aspects of the walls of the third ventricle just medial to the pillars of the fornices, approximately 8 mm. in length and less than 1 mm. in width. Each corpus Luysii was reduced to a narrow gray streak. The periaqueductal gray matter was finely granular, retracted, and unusually dark in color, these changes being more severe on the right where the area involved measured approximately 2.5 by 3 by 2 mm. in size. The lesion on the left was less severe but larger, lunate in

Fig. 7.—Case 3. Junction of midbrain and pons. Lesions in inferior colliculi, periaqueductal gray matter, and other structures of the tegmentum. (×2.)

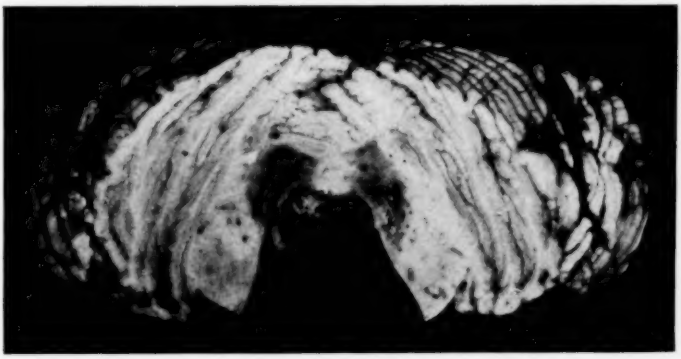

Fig. 8.—Case 3. Cerebellum. Symmetrical lesions in dentate nuclei. (×1.)

shape, and measured 3 to 4 mm. dorsoventrally and 2 to 3 mm. mediolaterally. They were separated from the lumen of the aqueduct by a narrow band of white tissue. There was a fusiform, granular, gray band of retracted tissue in each anterior corpus quadrigeminum, measuring 7 by 3 mm. on the right, and 5 by 2 mm. on the left. Similar changes were seen in the

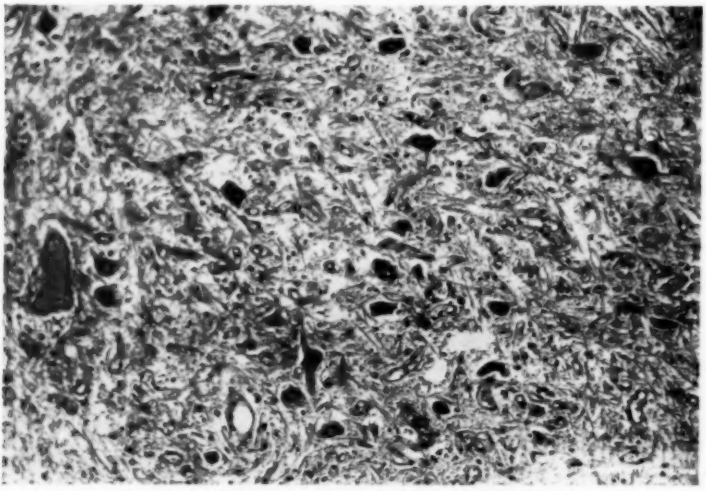

Fig. 9.—Case 3. Pons. Preservation of neurons in the severely affected fifth nerve nucleus. (H & E stain; ×150; reduced ⅕.)

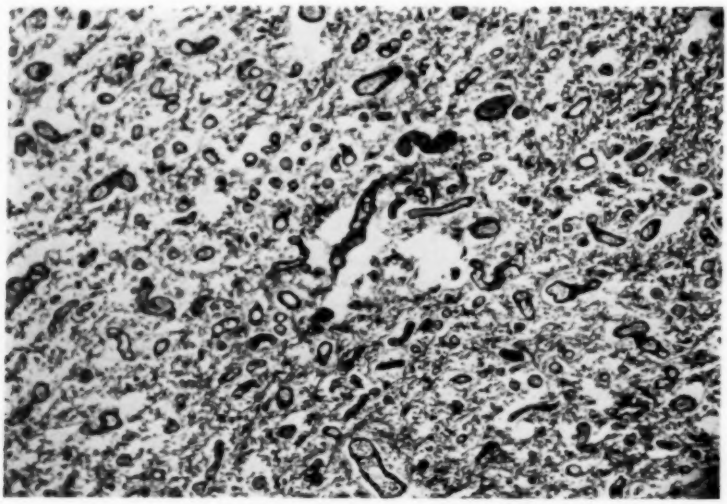

Fig. 10.—Case 3. Medulla. Marked vascularity in the degenerated eleventh nerve nucleus. (Laidlaw stain; ×150; reduced ⅕.)

posterior corpora quadrigemina (Fig. 7). Similar gray-pink retracted zones were present in the region of each third nerve nucleus and adjacent central tegmental tract. In the pons there were obliquely placed lesions 1 to 1.5 mm. ventral to the floor of the fourth ventricle in the region of the loci caerulei, measuring approximately 3 to 4 mm. in length and 1 to 1.5 in width. Similar bands of discoloration involved both superior olivary nuclei. The rostral medulla contained flame-shaped areas of gray discoloration in each twelfth nerve nucleus, extending toward the nuclei of Roller and others in the raphe, the medial lemniscus, and the central reticular formation. The mid-medulla revealed lesions involving the medial portion of each inferior olive and the central reticular substance above them. Areas of gray discoloration were present more caudally, involving the eleventh and supraspinal nuclei and the central reticular formation above them. In the cerebellum, each dentate nucleus appeared reduced in size and gray in color (Fig. 8).

Microscopically, the most severe lesions were those involving each dentate nucleus and adjacent tissues of the cerebellar central white matter, in which areas the destruction of tissue resulted in the formation of cavities. Other lesions were found in the optic chiasm, the inferior colliculi, the substantia nigra, the nuclei of the fourth, fifth (Fig. 9), sixth, eighth, ninth, tenth, eleventh (Fig. 10), and twelfth cranial nerves, the inferior olives and other scattered foci in the brain stem. The lesions were focal in character and characterized by a partial or complete loss of neurons. In places, normal

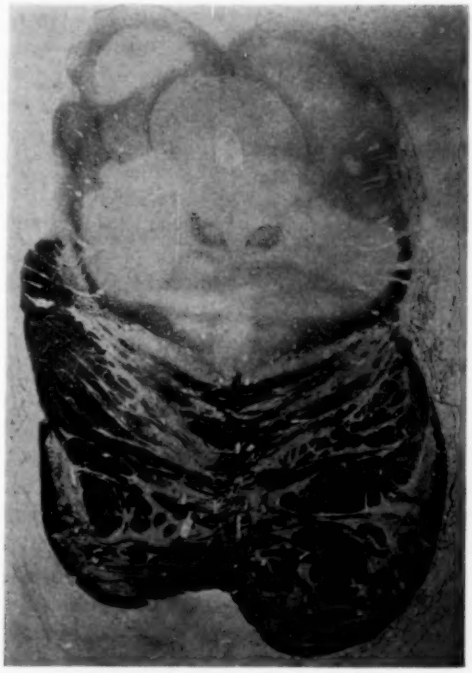

Fig. 11.—Case 3. Junction of midbrain and pons. Loss of myelin sheaths in a large area of the tegmentum. (Mahon stain; ×5; reduced ⅓.)

neurons were preserved in a devastated zone. In some lesions, the neurons were somewhat shrunken and deeply staining, while in other lesions, notably in the substantia nigra, the cerebellum, and the inferior olives, the neurons showed acute chromatolytic changes. There was some loss of axons, but considerably less than the loss of myelin sheaths, which was extensive (Fig. 11). An increase in astrocytes and glial fibers was present in a few lesions, notably in the inferior olives, but was only slight in most. The astrocytes were generally small, except for some hypertrophied cells in the areas in which acute neuronal changes were evident. A slight proliferation of microglial cells was noted, which did not attain the appearance of phagocytes. The blood vessels appeared to be increased in number within the lesions and were somewhat tortuous. In most instances, the blood vessel walls appeared normal. In a few instances, a slight hyperplasia of endothelial cells was present, and a moderate increase in connective tissue fibers were noted. There were no hemorrhages and no deposits of blood pigment.

Summary.—This 4-year-old female child died after a slowly progressive disease of insidious onset characterized by a failure of normal growth and development, slight mental deficiency, strabismus, intermittent nystagmus, a generalized ataxia, a generalized tremor, muscular weakness, and hypotonia. At autopsy, bilaterally symmetrical lesions were found in the walls of the third ventricle, the periaqueductal areas, the floor of the fourth ventricle, the dentate regions of the cerebellum, and the optic chiasm. Microscopically, a partial loss of neurons was noted, with acute chromatolytic changes in some of the preserved cells, a marked loss of myelin sheaths, a slight loss of axons, a slight astrocytosis, and a marked increase in the number of dilated tortuous capillaries with hyperplastic, somewhat fibrotic walls.

DISCUSSION

Although only two of the three cases originally described by Wernicke[1] occurred in conjunction with chronic alcoholism, the toxic effects of alcohol were implicated for many years as the primary etiological factor in Wernicke's encephalopathy.[2, 3] More recently, large numbers of cases have been described in nonalcoholic persons under circumstances that suggest a nutritional deficiency. The disease has occurred in prisoners of war whose dietary intake was inadequate, especially in thiamine.[4, 5] Cases have been reported in patients with severe diseases of varying character, as in long-standing fever,[10] in surgical practice,[9] and especially in disorders of the gastrointestinal tract.[6-8] Some changes occurring in pregnancy have been considered to be of similar character.[28] Anorexia has been frequently emphasized in these cases. Impaired absorption of thiamine may be an additional factor in gastrointestinal disease, while the febrile cases may have required increased quantities of thiamine for their metabolism. Clinical improvement resulting from thiamine therapy has been reported.[4-7]

Thiamine deficiency is indicated by the increase in the concentration of pyruvic acid in the blood, a substance normally metabolized under the influence of thiamine pyrophosphate (cocarboxylase).[29, 30] Hyperpyruvemia has been observed in oriental beriberi,[30, 31] in peripheral neuritis,[32] and in Wernicke's encephalopathy.[21] In each instance, thiamine therapy was associated with clinical improvement and with a decrease in the abnormally high blood pyruvate levels.

Pathologic changes resembling Wernicke's encephalopathy have been produced by thiamine-deficient diets in the pigeon,[15-19] rat,[11] fox,[13, 14] monkey,[33] and cat.[34] In the fox, the disease often resulted from the destruction of the thiamine normally present in the ration by an enzyme in fresh fish added in some seasons.[35]

In human beings, the conditions which give rise to thiamine deficiency are also likely to result in deficiency of other vitamins, such as nicotinic acid.[36] Such multiple deficiencies may result in mixed syndromes so that the limits of each may be difficult to delineate. It is generally agreed that the ophthalmoplegia responds to thiamine therapy more rapidly than do other aspects of the Wernicke syndrome.[37] The Wernicke syndrome has been considered to be the result of deficiencies of a number of substances[37, 38] or of thiamine alone,[16] depending in part on the definition of the syndrome.

The situation is further complicated by the fact that at least four syndromes have been related more or less specifically to thiamine deficiency (i.e., beriberi, polyneuritis, Wernicke's syndrome, and the Korsakoff syndrome). Polyneuritis is probably the most common and has been said to result from thiamine deficiency of lesser intensity than that which produces the Wernicke syndrome. Jolliffe, Wortis, and Fein[38] reported peripheral neuritis always to be present in cases of Wernicke's encephalopathy. However, Campbell and Russell[7] report that only nine in their series of twenty-one cases of Wernicke's encephalopathy showed evidence of such changes. More recently, doubts have been expressed as to the etiological relationship between thiamine deficiency and peripheral neuropathy.[39] Beriberi, which is most typically the result of thiamine deficiency, is not customarily associated with Wernicke's encephalopathy, and the latter is not usually accompanied by the former. Reference has already been made to the possible influence of other vitamins, such as nicotinic acid.[36] Other factors, such as an endogenous toxin,[40] have also been suggested.

The occurrence in children of a disease process like that described in this paper was first reported by Segawa[23] in Japan in 1916, as "breast milk intoxication." Nervous symptoms in a breast-fed infant whose mother "did not have beriberi" cleared with supplementary feedings. In 1918 Karasawa[24] described pathologic changes, which were apparently not characteristic, in two such cases. The first complete description is that of Tanaka.[25] After reviewing the Japanese literature, he described the case of a 5½-month-old male child with generalized weakness, acute palsies, rigidity of all limbs, hyperactive patellar reflexes, bilateral Babinski signs, generalized ataxia, convulsions, and coma. This child was being breast fed without dietary supplements by a mother who showed no specific evidence of avitaminosis, but who was nephritic. At autopsy, lesions were noted primarily in the nuclei of the third, fourth, fifth, ninth, and tenth cranial nerves, and the colliculi. These were characterized by rarefaction, small focal hemorrhages, an apparent increase of the number of hyperplastic, tortuous capillaries, a decrease in the number of neurons, with those remaining showing swelling and chromotolysis of the cytoplasm, which was occasionally eosinophilic, and irregular, shrunken, ec-

centric nuclei. In addition, focal hemorrhages with hyperemia but without neuronal changes were noted in the corpus striatum, the cerebellum, and to a slight extent in the cortex. More recently Guerrero[27] reported clinical observations on two children in the Philippines, 16 and 10 months old, respectively, with weakness, somnolence, and ocular palsies in both, and ataxia in the former. In each instance, the symptoms followed an acute febrile illness. Both children had been breast fed without adequate supplementary foods and were considered malnourished. In the second case, the infant received potatoes, rice, gruel, bananas, and halibut liver oil, supplemented by thiamine until two months prior to admission. The symptoms cleared rapidly on thiamine therapy, later supplemented by B complex preparations. Leigh[41] has described the findings in an 8-month-old infant who appeared entirely normal until six weeks prior to death. He had been breast fed for the first six weeks and then put on complementary feedings. The clinical features included somnolence, an apparent loss of vision and hearing, small nonreactive pupils, bilateral optic atrophy, spastic extremities, bilateral Babinski reflexes, and a loss of deep reflexes. He died three days after hospitalization with a terminal hyperpyrexia. At autopsy, the only abnormalities noted were in the nervous system. Bilaterally symmetrical areas of dark gray-brown discoloration were noted in various portions of the thalamus, the substantia nigra, the red nuclei, the periaqueductal area, the corpora quadrigemina, the tegmentum of the pons, the inferior olives, the central gray matter of the lower medulla, and the posterior columns of the cervical and thoracic cord. Microscopically, the most striking change in these lesions was a marked proliferation of capillaries, small arterioles, and small venules, the walls of which were not thickened. The affected zones were rarefied. Some of the neurons showed degenerative changes, which included "swelling of the cell body with cell chromatolysis and nuclear swelling, generalized cell shrinkage neuronophagia and satellitosis." The persistence of normal neurons in the affected areas was specifically described, and this was strikingly true of the trochlear nuclei. There was a marked proliferation of microglial cells and astrocytes, with areas in which a marked increase in glial fibers were noted. The oligodendroglia were decreased in number. The lesions were generally demyelinated, and this was particularly evident in sections of the optic nerves and tracts and of the dorsal columns of the cord. The mammillary bodies were unaffected. This is clearly the same pathologic entity as is described in the cases being presented here. Leigh had noted the striking similarity between the tissue reaction in his case and that found in Wernicke's syndrome, although he pointed out certain differences in the distribution of the lesions, particularly their absence in the mammillary bodies and their presence in the spinal cord in his case.

Campbell and Russell[7] reported the presence of acute lesions resembling those of Wernicke's encephalopathy in the mammillary bodies and other parts of the hypothalamus of a 3½-year-old child. This occurred after an acute illness characterized by listlessness and anorexia for two weeks, a slight cough and occasional vomiting for one week.

and fever, headache, and hallucinations for three days. These authors stated that in this case there was nothing to suggest a dietary deficiency. This differs from the other reported cases in that it is acute, rather than chronic and progressive.

The children presented in this paper showed pathologic changes, the character and distribution of which resemble those of Wernicke's encephalopathy as previously reported. The apparent vascular proliferation (Figs. 2 and 10), rarefaction of the tissue, neuronal degeneration (Fig. 4), the persistence of relatively normal neurons in severely devastated zones (Fig. 9), and the variable astrocytosis are all features constantly described in this condition. Demyelinization, which is prominent in our material (Figs. 5 and 10), is not specifically described in most other studies. A few report the absence of demyelinization. Myelin is generally considered to be susceptible to even relatively minor degrees of injury of almost any type, and its loss would be expected in a zone of degeneration of the sort described.

The lesions in these cases are more chronic than in most typical examples of Wernicke's encephalopathy. Only a rare fresh hemorrhage was observed, for example (Fig. 2). However, four of the twelve cases in Campbell and Biggart's original report[6] were considered "subacute," and in the subsequent report of twenty-one cases,[7] including these twelve, two cases of "healed" Wernicke's encephalopathy were described. These showed essentially atrophy and gliosis of the mammillary bodies, which these authors considered most characteristic. Neubürger[40] reported similar healed cases. Mayer[42] also reported chronic lesions in the form of marked gliosis and of vascular calcification.

In general, the lesions were concentrated in the periaqueductal region, the walls of the third ventricle, and the floor of the fourth ventricle, but involved deeper structures as well. In none of the present three cases, nor in that of Leigh[41] were changes in the mammillary bodies observed, although this is considered the most common site of lesions in Wernicke's encephalopathy. Nonetheless, it was not involved in Tanaka's case,[25] nor in two of twenty-three cases reported by Riggs and Boles[22] in which this region was examined. The thalamus was involved in one of the present cases, the subthalamus in the two others. Lesions were present at sites which are less commonly involved, although reports of similar involvement in cases of Wernicke's encephalopathy are easily found in the literature. The substantia nigra was involved in all three cases, in Leigh's[41] case and in one in Campbell and Russell's[7] series, an acute case in which there was known dietary deficiency. The inferior olive was involved in two of our cases, in Leigh's case,[41] and also in four of Mayer's[42] cases and eleven cases described by Riggs and Boles.[22] The superior cerebellar peduncle was involved in one of our cases and the inferior cerebellar peduncle, the dentate nucleus, and the adjacent central cerebellar white matter in another. The cerebellum was involved in two of Campbell and Russell's[7] cases, in one of Mayer's[42] cases, in at least four of Bender and Schilder's[3] cases, and in three cases reported by Riggs and Boles.[22] Of special interest is the involvement of the optic chiasm and

tracts in two of our cases, in Leigh's[41] case, and of the optic nerves in one of Mayer's[42] cases, and in two of Campbell and Russell's[7] cases. Campbell and Russell[7] described involvement of the fornix in seven cases, Riggs and Boles[22] in three. The latter authors also described involvement of the septum pellucidum in nine cases and the corpus callosum in one. Leigh[41] reported the dorsal columns of the cord to be affected in his case. It would appear that the disease is not limited to the gray matter, nor is it as diagrammatic in the distribution of its lesions as is sometimes pictured. It must be added that in most of the cases quoted, illustrating the less common localization of lesions, a nutritional deficiency was present to support the diagnosis. However, Campbell and Russell[7] expressed some doubt as to the nutritional character of the disease in one of the two cases of optic nerve involvement and two of the seven cases of involvement of the fornix referred to previously, although they considered the process, nevertheless, to be that of Wernicke's encephalopathy. Leigh felt "slightly more in favor of a deficiency disorder" as the pathogenetic factor in his case, but noted that the evidence for this was far from conclusive.

The pathogenesis of the process is obscure. There are some, such as Alexander,[16] who believe the primary injury is to the blood vessels. It is true that the vascular changes are the most striking, but it is less obvious that they are the most fundamental. In most areas the vessel walls are thin and appear essentially normal, and it is possible under such circumstances that the increased number and tortuosity of these vessels are more apparent than real, reflecting the condensation resulting from destruction of other tissue components. In some areas, a slight to moderate cellular hyperplasia of the vessel walls, often with an increase in connective tissue fibers, indicates a pathologic change in the vessels so that there might be a true increase in their number. In any case the suggestion that the other changes in the neurons and fibers, and subsequently in the microglia and astrocytes, are secondary phenomena due to ischemia is difficult to accept, at least as the sole factor. The persistence of intact neurons in devastated areas (Fig. 9) is quite remarkable and would be less likely to occur in ischemic encephalomalacia in view of the marked sensitivity of neurons to this deprivation.

The occurrence, though infrequent, of lesions in the white matter, as well as the severity of other changes where neurons persist, suggests that neuronal damage is not the sole factor. It would appear rather that many of the constituents of nervous tissue, including neurons and blood vessels, and probably other elements such as the astrocytes, which seem to suffer and fail to react, are directly affected by the pathologic factors. The peculiarly selective distribution of the lesions is certainly significant. The bilateral symmetry is often very striking (Fig. 1), as is the tendency to spare a thin layer of tissue adjacent to the ventricular surface (Figs. 1 and 3). The mechanisms that result in these unusually distributed lesions remain obscured by our fundamental ignorance of many basic processes in neural tissue. It is only a more extreme example of the difficulty experienced in ac-

counting for the localization of many pathologic processes.

Most of the lesions appear old and quiescent, the remains of a once active pathologic process. In the medulla described in Case 2, and the medulla and cerebellum in Case 3, acute changes are recognized in neurons, which appear swollen and pale, with a loss of Nissl substance and eccentric nuclei (Fig. 4). In Case 1, very rare small hemorrhages are noted (Fig. 2). In all cases, there is a slight hyperplasia of the endothelial cells of some of the vessels. This is scarcely convincing evidence that the fundamental pathologic process is continuing, but it does suggest this possibility. The clinical data are not too helpful in this respect. The process was insidious in onset and, at all times, was characterized by an obscure, very slow progression of symptoms and signs. In two cases death was due to intercurrent infection, while in one (Case 2) death was unexpectedly sudden and was not associated with any significant visceral changes.

In general there is comparatively little astrocytosis in these lesions so that most appear rarefied. It would seem that the astrocytes are generally impaired in their activities by the same factors that destroy the neurons. In some of the older lesions the number of shrunken astrocytes present may be somewhat in excess of that which may be attributed to condensation of the rarefied tissues. In the optic chiasm these astrocytes are piloid in shape. However, the number of glial fibers found is relatively small, except in isolated instances, such as the inferior olives in Case 3. Although the degree of astrocytosis may vary widely even in the same groups of diseases (e.g., diffuse sclerosis), it is of some interest that in subacute combined degeneration, which is certainly a metabolic disorder, the degree of astrocytosis is consistently minimal.

In view of the lack of evidence of dietary insufficiency, the age group, and some variation in localization, some thought must be given as to whether these cases may validly be considered examples of Wernicke's encephalopathy. This question is in part pathological and in part philosophical. Biological processes do not follow a rigid mold, but rather a general pattern, the limits of which are not clearly defined. In cases where the etiological factors are obscure, the segregation of cases forming a disease entity is doubly difficult. The three cases reported are similar in the character of the pathologic process to those cases of Wernicke's encephalopathy of a subacute and chronic type, and the distribution of their lesions even more closely resembles the classical disease.

The possibility that these might represent cases of kernicterus was considered. All such persons are jaundiced shortly after birth, and, in many, evidence of Rh incompatibility may be obtained. Most infants so affected die shortly after birth, but there are a number of reports[43, 44] which suggested that in many of the milder cases the infant may survive for a considerable period with neurological sequelae. These usually include decreased intelligence, hypotonia or rigidity, involuntary motor activity, and sometimes deafness. There are comparatively few reports of autopsy findings on persons surviving for an appreciable period. Among these may be included the reports of de Lange[45] and Zimmerman and Yannet.[46] In

general, the pigmentation of nuclear masses is not observed in infants living more than a few months, but loss of neurons and of nerve fibers in the globus pallidus, neostriatum, subthalamic nuclei, and hippocampal gyri, and, less frequently, in the thalamus, red nuclei, cerebellum, floor of the fourth ventricle, and substantia nigra is seen. Histologically, such lesions do not show the vascular changes characteristic of Wernicke's encephalopathy and of the cases reported here. The absence of jaundice at birth, and the progressive character of the disease in the present condition, also tend to exclude such a diagnosis.

Infantile encephalomalacia of the type described by Winkelman and Moore[47] and others[48-50] deserves mention because these cases also are of obscure pathogenesis and are characterized by encephalomalacic changes. The involvement is limited to the cerebrum, sparing the cerebellum and brain stem, and is characterized by the formation of large cavities. The infants die in a few months.

The distribution of lesions in the present cases is in some respects similar to that in cases of olivo-ponto-cerebellar atrophy, in some of which there is involvement of other structures as well.[51] Isolated reports have implicated the cortex, spinal cord, basal ganglia, substantia nigra, thalamus, and subthalamus. These cases occur characteristically in older persons and are slowly progressive. Involvement of the cerebellar cortex, pons, and the olives are most severe, and gross atrophy of some of these structures is often evident. Histologically, neuron loss, reactive gliosis, and destruction of fiber tracts are usually described. The type of vascular change seen in Wernicke's encephalopathy and in the infants reported here is not described. It is a system disease, although perhaps poorly defined, and is not characterized by scattered focal lesions such as are here presented.

The relationship between the disease process in the cases being reported and thiamine deficiency is less clear than in many of the reports on adult cases and in experimental studies. The infant in Case 1 was offered Dextri-Maltose and cereals and, at 5 months, liver and thiamine. He is said to have regurgitated part of his feeding and to have refused foods offered to him. Following thiamine therapy, partly parenteral, the feedings were better tolerated, but nutrition was considered below average. Nutritional data are not available on the infant in Case 2. The child's parents are educated and of a good economic status, and it is probable that this child was offered as good a diet as his sister (Case 3). At autopsy, the body of the second child appeared well nourished. The third child is known to have been offered an adequate diet which included vitamin supplements. Appetite is described as poor, with periods of frequent vomiting noted at about 10 to 12 months of age. The first significant clinical sign, a marked transient internal strabismus, appeared at 6 months. Although development was impaired, nutrition was considered good. In general, it cannot be claimed that convincing evidence for a dietary etiology in these cases is available. One gains the impression that the anorexia was the result, not the cause, of the disease process.

Other reports also suggest instances in which a dietary etiology for Wernicke's encephalopathy is questioned. In four of the twenty-one cases reported by Campbell and Russell[7] the authors felt that "the probable existence of deficient vitamin intake was not so obvious," and in two of these, "we could see no reason for such a deficiency."

Thiamine deficiency despite an otherwise adequate diet may occur when the requirements for thiamine are unusually high, as in continued febrile states, or when absorption of thiamine from the food is impaired by disease of the gastrointestinal tract. We might postulate a mechanism which would theoretically result in the same physiologic and even pathologic changes as in thiamine insufficiency. It is known that thiamine is normally phosphorylated, and the resulting thiamine pyrophosphate acts as coenzyme in the metabolism of pyruvic acid. If one or several of such chemical reactions were impaired by some unrelated metabolic disorder, the result might be indistinguishable from the impairment of such a chemical reaction due to thiamine deficiency. We might look upon such an alteration as a congenital physiologic malformation, analogous to the more common congenital morphologic malformations. This appears to be true in cases of alcaptonuria and phenylpyruvic oligophrenia. The occurrence of the disease in siblings in two of the present cases, associated with parental consanguinity, tends to support this concept. However, no direct evidence for the existence of such a postulated metabolic defect is available.

SUMMARY

1. Three cases are reported of children succumbing to a disease process resembling Wernicke's encephalopathy.

2. There is no convincing evidence of a dietary inadequacy of thiamine or other vitamins, nor of a difficulty with intestinal absorption, nor of an abnormally high thiamine requirement in these cases.

3. Two of the patients were siblings of a consanguineous marriage. It is suggested that a congenital metabolic disorder, possibly involving the utilization of thiamine or in the enzymatic processes with which thiamine derivatives are concerned, may be present in these cases.

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MENINGOCOCCAL INFECTIONS; WITH PARTICULAR REFERENCE TO FULMINATING MENINGOCOCCEMIA (WATERHOUSE-FRIDERICHSEN SYNDROME) TREATED WITH CORTISONE AND NOREPINEPHRINE

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RECENT public health reports suggest that a major epidemic of meningococcal disease may be expected within the next year. Epidemics of meningococcal infection have occurred about every nine to ten years and are usually preceded by one or two years of gradually increasing incidence. In the past two years reports from the Armed Forces and civilian groups have shown an increasing incidence of illness due to the meningococcus.[1] The most recent major epidemic occurred in 1943.

The present report reviews thirty-six patients hospitalized for meningococcal disease. These patients were admitted to the Pediatric Service of the Jefferson Davis City-County Hospital during the twenty-one-month period from January, 1952, through September, 1953. In 75 per cent of the patients the organism was identified; in the remaining 25 per cent the clinical diagnosis was not verified by bacteriologic study. Included in the series are five critically ill children with acute meningococcemia and shock (Waterhouse-Friderichsen syndrome), three of whom survived.

The Waterhouse-Friderichsen syndrome is being considered as a separate section of this report since the clinical picture, management, and prognosis differ widely from other complications of meningococcal infection.

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MENINGOCOCCEMIA

Clinical Manifestations.—

Symptomatology: The presenting symptomatology is summarized in Table I.

Fever. A temperature elevation in the range of 103° to 105° F. was present in all but one patient. The latter was admitted in shock with an admission temperature of 97° F.

TABLE I. THE PRESENTING SIGNS AND SYMPTOMS OF THIRTY-SIX PATIENTS WITH MENINGOCOCCAL INFECTION

	NO. OF PATIENTS
Fever	35
Skin lesions	30
Nuchal rigidity	26
Vomiting	21
Headache	10
Arthritis	7
Convulsions	3

Skin Lesions. Skin lesions, of which the majority were petechial, were present in 83 per cent of these patients. Several had large ecchymotic lesions, and in one patient, who had extensive skin necrosis, skin grafting was eventually necessary. A few patients presented an erythematous, papular rash, without evidence of hemorrhage, as described by Hill and Lever.[2] It is worthy of note that diagnosis was delayed in one of the fatal cases be-

cause of the absence of any demonstrable skin, conjunctival, or retinal lesions. At necropsy, bilateral adrenal hemorrhage was present and *Neisseria intracellularis* was grown from the ante-mortem blood culture.

Arthritis. Arthritis was a presenting problem in 20 per cent of these patients. One patient was admitted as a "probable acute rheumatic fever," with low-grade fever and a swollen, tender knee. The correct diagnosis was established only when a blood culture was reported as growing *N. intracellularis.* This patient recovered promptly on antibiotic therapy.

Clinical Type: The clinical type of meningococcal disease is illustrated in Table II. The larger group presented clinical manifestations of bacteremia as evidenced by the presence of peripheral emboli, and/or blood culture positive for *N. intracellularis.* The smaller group of six patients had no evidence of bacteremia clinically or by culture of the blood. In these patients, the involvement appeared clinically to be limited to the central nervous system.

Age and Sex: Twenty-five patients were males and eleven females, a predominance of male over female in ratio 2:1. The age varied from 1 to 13 years. Fig. 1 graphically shows the age of the patients in this series. This age distribution is similar to that given in standard textbooks of pediatrics.[3] Twenty of these children were white and sixteen were Negro. This almost 1:1 ratio is an interesting finding since the usual ratio of white to Negro children admitted to this hospital is more nearly 1:3. Two families contributed six of the patients in this series, four in one family and two in the other.

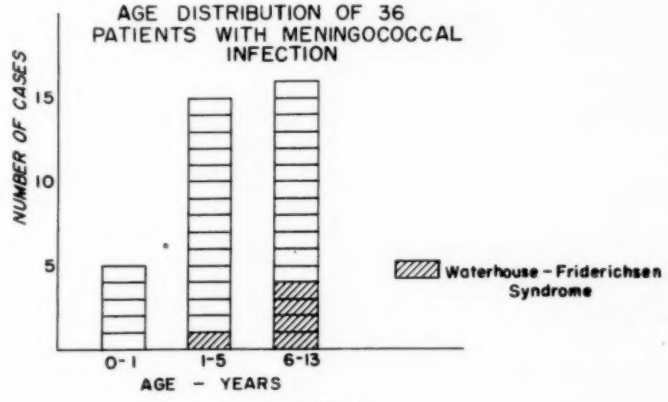

Fig. 1.

Seizures. In only three patients were convulsions a presenting symptom.

TABLE II. CLINICAL TYPES OF MENINGOCOCCAL DISEASE IN THIRTY-SIX PATIENTS

		NO. OF CASES
Meningococcemia		30
With meningitis	19	
With Waterhouse-Friderichsen syndrome	5	
Uncomplicated	6	
Meningitis without demonstrable meningococcemia		6
Total		36

Diagnosis.—Bacteriologic identification of *N. intracellularis* was possible

in 75 per cent of the patients (Table III). In four instances, the etiological agent was identified by Gram's staining of material obtained from the patient's skin lesions, according to the method of Tompkins.[4] In two of these patients, this was the only method by which the organism was demonstrated. Sporadic antibiotic or chemotherapeutic treatment had been given to many of the patients prior to the time they were admitted to this hospital. This

TABLE III. METHOD OF ESTABLISHING DIAGNOSIS IN THIRTY-SIX PATIENTS WITH MENINGOCOCCAL DISEASE

		NO. OF CASES
Bacteriologic confirmations		27
Positive blood cultures	8	
Positive spinal fluid culture	18	
Organisms demonstrated in skin lesions	4	
Clinical picture alone		9
Total		36

fact, along with the known difficulty in culturing *N. intracellularis*, may account for the nine cases in which no bacteriologic confirmation was obtained. All patients included in this series were either proved by bacteriologic methods, or the clinical picture was sufficiently typical to warrant a diagnosis of meningococcal infection.

Complications.—The complications seen in these thirty-six patients are shown in Table IV. Arthritis was the most prevalent complication in this

TABLE IV. COMPLICATIONS ENCOUNTERED IN THIRTY-SIX PATIENTS WITH MENINGOCOCCAL DISEASE

	NO. OF CASES
Arthritis	4
Subdural effusion	1
Corneal ulcer	1
Slough of skin lesion, necessitating skin grafting	1

series, occurring in about 10 per cent of the patients. In other reported series, this complication has been noted in from 5 to 20 per cent.[5-7] In the four patients in whom arthritis developed, the swelling, pain, and increased temperature persisted from a few days to as long as three weeks in one instance. The joints involved were usually the large joints, such as the knee or elbow. Fluid was aspirated from the joint space of the more persistent cases (three patients) and was found to be sterile on culture. All patients eventually responded, and follow-up roentgenographic examination showed no evidence of permanent joint deformity. Subdural effusion was found in only one patient. It cleared following repeated needle aspiration through the anterior fontanel. The relation of the necrotic skin lesion to the use of norepinephrine is not clear. The fact that tissue necrosis may occur following subcutaneous leakage of norepinephrine from an intravenous infusion, however, is well established.[8]

Prognosis.—Two (5 per cent) of the thirty-six patients died; all others recovered satisfactorily. These two patients presented the clinical picture of meningococcemia and associated shock (Waterhouse-Friderichsen syndrome). Both of these patients had positive ante-mortem blood cultures, and both were found to have massive, bilateral adrenal hemorrhage at necropsy. One of the two children had no skin lesions or abnormal spinal fluid findings and was diagnosed only after necropsy. The second patient died shortly after reaching the isolation division. Definitive therapy was not instituted in either case.

WATERHOUSE-FRIDERICHSEN SYNDROME

In 1938, Christian[9] made the statement that all known cases of the Waterhouse-Friderichsen syndrome (W-F syndrome) had been fatal, usually within twenty-four hours of onset. This syndrome is said to occur in 2 to 4 per cent of all cases of meningococcemia with a greater frequency in children. It is usually associated with *N. intracellularis* infection, but occasionally the streptococcus, pneumococcus, or staphylococcus has been incriminated. In 1940, following the advent of the sulfonamides, Carey[10] reported the survival of a patient with clinical evidence of the W-F syndrome. Subsequent to this report, occasional instances of recovery following penicillin and sulfonamide therapy have appeared. Adrenal cortical hormone preparations in the form of desoxycorticosterone and aqueous extract of the adrenal cortex have been used sporadically. The value of these preparations in the management of patients with the W-F syndrome is debatable. In 1951, Nelson and Goldstein[11] reported the use of cortisone, in addition to antibiotics and other supportive measures, in the successful treatment of two patients with W-F syndrome. Since that time, scattered reports have appeared concerning patients who have survived following the use of combined cortisone and antibiotic therapy.[12-19]

Clinical Picture.—The clinical picture of the W-F syndrome is characterized by the evidence of an acute infection with profound circulatory collapse. The symptoms of the invasive phase resemble those of many acute infections, namely, fever, malaise, headache, generalized aching, and sometimes chills and vomiting. In a matter of hours the patient becomes increasingly toxic and more febrile. This is followed by profound circulatory collapse. The latter is characterized by striking cyanosis and lividity of the dependent parts, with marked hypotension which may progress to "irreversible shock" and coma. Death usually occurs within twenty-four hours.

Five of the patients in this series presented the clinical picture of the W-F syndrome; the two deaths occurred in this group.

CASE REPORT

The following case report is that of a patient with W-F syndrome who survived. She was treated with antibiotics, cortisone, norepinephrine, and general supportive measures.

A 13-year-old Negro girl was seen at the Jefferson Davis City-County Hospital with the chief complaint of a skin rash of some twelve hours' duration. The history revealed that she had been well until five days before admission, when she was sent home from school because of a cough and low-grade fever. The fever continued, but she did not appear to be severely ill until one and one-half days before admission when her temperature suddenly increased; she complained of headache and vomited on two occasions. During the twelve hours prior to hospitalization, she remained in bed and experienced several chills. At the same time a fine rash appeared over the arms and legs. These skin lesions were noted to be purpuric on the morning of admission, and it was this feature that prompted the parents to seek medical attention.

Physical examination on admission revealed an acutely and critically ill child. She appeared to be delirious and was tossing about violently on the bed. Temperature was 104° F., pulse 150, respiration 56, blood pressure 53/35. There were many petechiae and ecchymoses of the skin surfaces and on the mucous membranes. The largest ecchymotic area was 4 cm. in

diameter. The skin showed mottling, particularly over the extremities. Her nail beds were slightly cyanotic. The deep tendon reflexes were hyperactive but equal bilaterally. Nuchal rigidity and tightness of the hamstring muscles were noted.

Laboratory studies revealed hemoglobin, 10.7 Gm. per cent; red blood cells, 3.9 million; white blood cells, 17,000 with 76 per cent polymorphonuclears, 21 per cent lymphocytes, and 3 per cent eosinophils. Gram-negative diplococci were identified in the peripheral blood smear. Urinalysis revealed only a trace of albumin. Gram-negative diplococci were identified in material obtained from the patient's skin lesions. A lumbar puncture was performed (the initial pressure was 212 mm. of water and the final pressure was 204 mm. of water). Nine cubic centimeters of cloudy spinal fluid was removed. This fluid contained 234 cells per cubic millimeter, of which 90 per cent were polymorphonuclears. The protein content was 81 mg. per cent, chloride, 123 meq. per liter. Within thirty-six hours, *N. intracellularis* was cultured from this spinal fluid.

Immediately following the lumbar puncture, one million units of penicillin and 2 Gm. of sodium sulfadiazine (as a 5 per cent solution) were given intravenously. An intravenous infusion of 4 mg. norepinephrine in 1,000 c.c. normal saline was begun. The rate of infusion was adjusted so as to maintain the blood pressure above shock level. In this manner the blood pressure was elevated from the admission level of 53/35 mm. Hg to systolic levels of 85 to 100 mm. Hg. Almost immediately the patient's general condition improved, although her sensorium remained cloudy for the first twelve hours. During this period the temperature fell from 104° to 101° F.

Subsequent therapy included 500,000 units of aqueous penicillin intramuscularly every two hours; 1 Gm. of sodium sulfadiazine (in a 2½ per cent solution) by hypodermoclysis every four hours; and 50 mg. of cortisone intramuscularly every six hours. A total eosinophil count twelve hours after admission showed 6 per cubic millimeter.

Twenty-four hours after admission, the patient was rational and asking for food. Norepinephrine was omitted from the intravenous infusion and the blood pressure stabilized at about 95/65 mm. Hg. Sulfadiazine by hypodermoclysis was discontinued, and oral sulfadiazine was begun. Cortisone dosage was gradually decreased over a period of the next five days and was discontinued on the fifth day. On the fifth hospital day the total eosinophil count was 175 per cubic millimeter.

Daily oral temperature elevations from 100° to 101° F. persisted, and on the sixth hospital day it was noted that the patient's left elbow was swollen, hot, and tender. Needle aspiration of this joint on the eighth hospital day produced 15 c.c. of cloudy yellow fluid which was shown to be sterile on culture. The temperature gradually returned to normal, and the elbow became asymptomatic. A lumbar puncture performed on the fourteenth hospital day was normal. Penicillin and sulfadiazine were discontinued at this time.

During the first two weeks of hospitalization the multiple skin lesions gradually cleared, with the exception of an area of confluent necrotic ecchymoses in the left antecubital region. The skin over this area sloughed, leaving a granular, denuded area 6 by 5 cm. in size. This lesion did not respond to conservative management, and skin grafting was necessary one month after admission. Excellent results were obtained. The patient was discharged after six weeks of hospitalization.

Two other patients in this series had essentially the same clinical picture. They were managed in a similar manner. Outcome in both was successful. This case was chosen to report in detail since it illustrates two complica-

tions of meningococcal infections, namely, arthritis and necrosis of the ecchymotic skin lesions.

MANAGEMENT

Meningococcal infection must be considered a medical emergency. When initially seen, all patients with skin lesions suggesting meningococcemia should be considered as having such until proved otherwise. A rapid but thorough history and physical examination are accomplished and the necessary cultures taken. A lumbar puncture is usually necessary to establish the presence of meningitis. As soon as possible, parenteral penicillin and sulfadiazine therapy is begun. It is the policy of the Pediatric Unit of this hospital to start a continuous intravenous infusion immediately in all patients suspected of having meningococcal disease. This serves as an avenue for the administration of fluids, and in the advent of circulatory collapse one is not faced with the often fruitless problem of attempting to introduce a needle into a collapsed vein. Intravenous fluid is usually continued for a minimum of twenty-four hours or until such time as the patient's blood pressure is considered stabilized.

In the event of circulatory collapse, norepinephrine has been used to maintain the patient's blood pressure. A solution is prepared by adding 4.0 mg. (4 c.c. of 1:1,000 solution) of norepinephrine per liter of isotonic sodium chloride. The rate of intravenous infusion is then adjusted so that the amount introduced is just sufficient to maintain the blood pressure above shock level. In three patients so treated it has been possible to discontinue the addition of norepinephrine to the infusion, after twelve to thirty-six hours. In addition to antibiotics and norepinephrine, cortisone has been given to those patients presenting the picture of the W-F syndrome. This is used as replacement therapy for the presumably hypofunctioning adrenal cortex and is given intramuscularly in doses of from 25 to 100 mg. every six hours. The cortisone can usually be discontinued after five to seven days. No untoward effects referable to the cortisone therapy have been noted.

In this series sulfadiazine and penicillin were used in all cases; Aureomycin, Terramycin, chloramphenicol, and streptomycin were used in several cases, in addition to sulfadiazine and penicillin for the period prior to specific bacteriologic diagnosis. Whole blood transfusions and other supportive measures have been used as indicated by the needs of the individual patient.

DISCUSSION

The W-F syndrome deserves special consideration. There is considerable difference of opinion as to the pathological changes present in the adrenal glands of patients with the W-F syndrome. Aegerter,[20] in 1936, reviewed fifty-five cases of the W-F syndrome from the literature and reported bilateral adrenal hemorrhage in fifty-one and unilateral hemorrhage in three. In contrast, Williams,[21] in 1942, reported hemorrhage in the adrenals of only nine of seventeen patients with W-F syndrome. Rich,[22] in 1944, was able to find an explanation for this difference of opinion. In thorough histological studies he found microscopic evidence of severe degeneration of the adrenal cortical cells in several cases of W-F syndrome not showing gross hemorrhage. From this unitar-

ian point of view, it seems evident that the pathological picture may be viewed as a process which may advance from reversible cellular degeneration toward obliterating hemorrhage or may stop at any intermediate point.

In considering the pathogenesis of the W-F syndrome it has been pointed out that adrenalectomized dogs survive for about seven days without replacement therapy. Unlike the course following the removal of the adrenal gland in an otherwise normal animal, however, it is evident in the W-F syndrome that the exhaustion of the adrenal cortex occurs incident to the stress imposed by severe infection. It seems to represent physiological ablation of the adrenal precisely when the need for its function is the greatest. The nature of shock in this condition appears to be different from that following trauma, hemorrhage, or even slowly developing adrenal insufficiency. It is not related simply to decreased blood volume or to electrolyte imbalance.

Cortisone in the management of the W-F syndrome was first reported in 1951.[11, 12] Since that time there have been sporadic case reports in the literature which support the validity and almost "miraculous" recoveries associated with its use in this condition.[12-19]

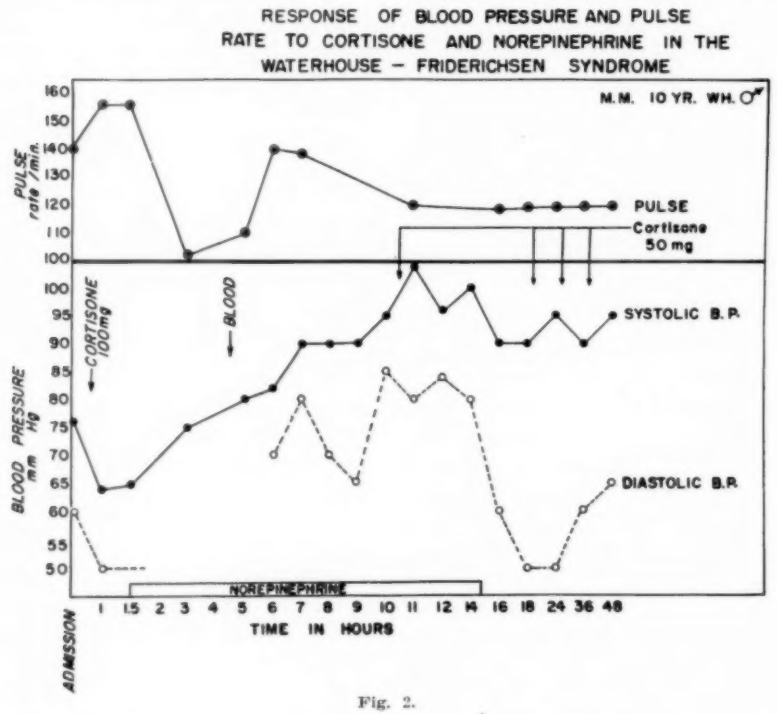

Fig. 2.

Two reports concerning the use of norepinephrine in the W-F syndrome have been found in the literature.[23, 24] Norepinephrine, when given in physiological doses, is an over-all vasoconstrictor with little influence upon car-

diac output. Its stimulant action on the central nervous system is minimal. Experimental evidence suggests that cortisone may potentiate the effects of norepinephrine.[25-29] Fritz[25] and Ramey[26] have demonstrated independently that in adrenalectomized experimental animals, adrenal cortical steroids are necessary for regular and repeated response of blood vessels to norepinephrine. Moyer and coworkers[23] have demonstrated the effectiveness of norepinephrine in maintaining an adequate blood pressure in patients with shock due to overwhelming infection by various bacteria.

These studies suggested that norepinephrine in conjunction with cortisone and antibiotics has a place in the management of patients with W-F syndrome. The three patients in whom this regime has been used have demonstrated the effectiveness of norepinephrine in elevating and maintaining the systemic blood pressure. Fig. 2 shows the response of the blood pressure and pulse rate of a 10-year-old white boy with W-F syndrome, treated in this manner. It seems probable that with this program of treatment, it may be possible to prevent profound shock and death in many patients with the W-F syndrome. Such encouraging results warrant a more extensive clinical evaluation of this therapy in patients with meningococcemia and associated W-F syndrome.

SUMMARY

1. The clinical course of thirty-six patients with meningococcal infection is presented.

2. Five patients in the series had the Waterhouse-Friderichsen syndrome.

A. Two of these patients died before therapy was instituted.

B. Three patients survived following treatment with antibiotics, cortisone, and norepinephrine.

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CONGENITAL HEART DISEASE IN A MEDICAL REHABILITATION PROGRAM

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GROSS,[1] in 1939, published the original report of his first successful surgical treatment of a patient with patent ductus arteriosus. Almost simultaneously in 1945 Gross[2] and Crafoord[3] published reports of the surgical correction of coaretation of the aorta. At about the same time Blalock and Taussig[4] reported the results of surgical treatment of pulmonary stenosis or pulmonary atresia. Also in 1945 Gross[5] first reported the surgical treatment of congenital vascular ring (double aortic arch). Thus, within a six-year period from 1939 to 1945, tremendous advances were made in the surgical correction of four types of congenital heart disease. Furthermore, it is possible that surgical closing of septal defects will become a safe and acceptable procedure within the near future.

Public health departments in the United States have been alert to take advantage of these newer surgical techniques in the development of special programs for children with congenital heart disease. For example, in the late 1940's, the New York City Department of Health paid for the hospital care of New York City children at the Johns Hopkins Hospital in Baltimore, Md., for the diagnostic workup and surgery of children with congenital heart disease. Shortly thereafter, facilities for cardiac surgery were developed in hospitals in New York City. The New York City program for children with congenital heart disease then began to develop more fully and on April 10, 1950, began to pay for care in approved hospitals in New York City. The following steps were taken:

1. *The establishment of a Cardiac Surgery Advisory Committee* to the New York City Department of Health. This Committee is composed of four members (two surgeons, a pediatric cardiologist, and a roentgenologist), all with experience in the diagnosis, surgical correction, and care of children with congenital heart disease. The members of this Committee have been appointed upon the recommendation of the New York Heart Association.

2. *The development of standards* of hospital care for children with congenital heart disease. These standards were set up with the assistance of the Cardiac Surgery Advisory Committee and must be reasonably met before a hospital can be approved under the Medical Rehabilitation Program of the

From the Bureau for Handicapped Children and the Bureau of Records and Statistics, New York City Department of Health.

This paper is the first of a planned series of two, the second one to be developed around services for patients with congenital cardiac anomalies admitted to the Medical Rehabilitation Program in upstate New York (the entire state exclusive of New York City). The second paper will follow at a later date under joint authorship from the New York State Department of Health and the Erie County Health Department.

Bureau for Handicapped Children of the City Department of Health. The standards require that the hospital provide a medical team with experience in the field of congenital heart disease consisting of a surgeon, cardiologist, roentgenologist, and anesthetist. Diagnostic facilities for x-ray, laboratory study, angiocardiography, and cardiac catheterization must be provided. There are additional requirements to be met: nursing staff, social service staff, the provision of an outpatient department, and affiliation with a convalescent institution in order to provide care for those children who require it after operation. These standards are currently being amplified.

3. *Payment for hospital care for children with certain kinds of handicaps,* among whom are children with congenital heart disease, by the Bureau for Handicapped Children of the City Health Department. Hospital care is paid for diagnostic work-up or surgery or both. Each hospital which is reimbursed has been surveyed by staff members of the Bureau for Handicapped Children and has been recommended for approval for participation in this program by the Department's Cardiac Surgery Advisory Committee. So far, ten hospitals in New York City are approved to participate in this program for children with congenital heart disease. One of these hospitals was recently approved and is not included among those discussed in this report. In addition, patients from New York City were referred to Johns Hopkins Hospital prior to 1950. But for the period covered by the study there were only nine participating hospitals, and the data in the paper are confined to those nine.

Approval is usually given for a maximum of seven days' hospital care for diagnostic work-up and of thirty days' hospital care for the preoperative, operative, and postoperative phases. In addition, special nurses, if necessary, may be paid for a three-day period following surgery. Extensions of all these services may be granted for an individual child, if indicated. Fees paid include a rate for hospital care at $10 a day ($13 a day now). In addition, the hospital is paid $35 for angiocardiography and $50 for cardiac catheterization. Convalescent care is not yet included under the New York City program. Inclusion of services for a six-week period has been recommended by the Cardiac Surgery Advisory Committee. Standards for convalescent care have recently been developed by the Public Health Committee of the New York Heart Association, and it is anticipated that convalescent care will be included shortly.[6]

This report will present data on the first 120 children with congenital heart disease who were cared for under the New York City medical rehabilitation program during a two-and-one-half-year period from April 10, 1950, to Oct. 1, 1952, plus nine children referred to the Johns Hopkins Hospital prior to April 10, 1950. The data are derived from a review of both New York City Health Department and hospital records. The report will attempt to answer certain questions of significance to public health workers responsible for the administration of programs for handicapped children:

1. How much of the affected population is being covered by the program?
2. How sound was community planning?
3. How complete was the service and did the children improve as a result of the service?
4. What are the costs and, basic to the costs, what was the length of hospital stay?

HOW MUCH OF THE AFFECTED POPULATION IS BEING COVERED BY THE PROGRAM?

In order to answer this question, it would be necessary to have complete facts on the incidence and prevalence of congenital heart disease in the community. At the present time such facts are not available in New York City and would be most difficult and expensive to collect. In lieu of this complete information, several leads are available to us.

Extent of Coverage of Children by the Medical Rehabilitation Program.—During the two-and-one-half-year period covered by this report (April 10, 1950, to Oct. 1, 1952) a total of 292 New York City children up to the age of 21 years who had congenital heart disease were admitted to the nine hospitals participating in the program. Of this number 120 (41.1 per cent) had their services completely or partially paid for in New York City hospitals by the Medical Rehabilitation Program (Table I). This extent of coverage by the program for only 41 per cent of the children would appear to be low. Possible explanations for this low percentage of coverage are: (1) limited dissemination of information about the program to the participating institutions, to the medical and allied professions, and to the public, (2) the determination of financial eligibility for care under the program based upon cost of living data which were out of date, (3) a very low per diem rate used by the program to provide payment for hospital care, (4) restriction of the program to the diagnostic and surgical phases of the care of children with congenital heart disease and exclusion of children who

TABLE I. EXTENT OF COVERAGE OF HOSPITAL CARE OF NEW YORK CITY CHILDREN WITH CONGENITAL HEART DISEASE BY MEDICAL REHABILITATION PROGRAM, APRIL 10, 1950, TO OCT. 1, 1952

HOSPITAL	DATE OF APPROVAL FOR PARTICIPATION IN MEDICAL REHABILITATION PROGRAM	TOTAL NUMBER OF NEW YORK CITY CHILDREN ADMITTED WITH PRIMARY CONDITION OF CONGENITAL HEART DISEASE	NEW YORK CITY CHILDREN COVERED BY MEDICAL REHABILITATION PROGRAM	
			NUMBER	PER CENT OF TOTAL
1	April, 1950	37	26	70
2	April, 1950	34	33	97
3	April, 1950	75	39	52
4	April, 1950	11	6	55
5	November, 1951	10	5	50
6	April, 1951	20	5	25
7	July, 1951	25	2	8
8	April, 1950	68	4	6
9	July, 1951	12	0	0
Total		292	120*	41

*An additional nine children from New York City were admitted to the Johns Hopkins Hospital under the Medical Rehabilitation Program.

may have needed conservative medical treatment, (5) hospital care given to some children with congenital heart disease prior to the time when they were approved to participate in the Medical Rehabilitation Program.

Age.—Table II shows the age of the children at the time of diagnostic work-up and of surgery. It is of interest that over one-half of the group referred for diagnostic work-up are of infant and preschool age, and about one-fourth are in the 5- to 9-year age group. There were only twenty patients in the age group of 10 to 19 years. While it is gratifying that proportionately more infants and preschoolers are being found and referred for care, some thought should be given to the relatively fewer referrals in the older age group. Obviously, those children with the very serious types of congenital heart disease may not have survived to reach adolescence. On the other hand, there must be additional older children with patent ductus arteriosus or coaretation of the aorta who could benefit from this program who should be found and referred for care.

TABLE II. AGE OF CHILDREN AT DIAGNOSTIC WORK-UP AND AT SURGERY

AGE	DIAGNOSTIC WORK-UP	SURGERY
Under 1 year	15	2
1-4 years	55	20
5-9 years	30	21
10-14 years	12	12
15-19 years	8	6
Other		8*
Unknown	9	
Total	129	69

*Eight children had two surgical procedures at the following ages:

Less than 1 year and 4 years	—1
At 2 and 3 years	—1
At 4½ and 6 years	—1
At 7 and 9 years	—1
At 9 and 12 years	—1
At 7 and 15 years	—1
At 11 and 13 years	—1
At 13 and 14 years	—1

HOW SOUND WAS COMMUNITY PLANNING?

Of the nine hospitals actively participating in the program and caring for the 129 children under the program, three hospitals cared for ninety-eight (76 per cent) of the children. The other thirty-one children in the program were scattered among the other six hospitals (Table I). This distribution of patients by hospital raises the question of whether the program has been wise in having so large a number of hospitals participate, or whether in retrospect it might have been more desirable to limit the number of hospitals. The advantage of limitation of the number of participating hospitals would be that more patients might be concentrated in fewer hospitals and, therefore, the hospital staff would have an opportunity of greater development of their diagnostic and surgical skills through greater case experience. The disadvantages of limitation of the number of hospitals would be twofold: (1) it might necessitate more traveling by the patient and his family because of geographic reasons, and (2) some children needing financial assistance might not receive it if they were cared for in nonparticipating hospitals. This particular problem is not confined alone to the care of children with congenital heart disease, but it is also being met in the program for children with orthopedic handicaps. The problem has great implications for program-planning for the future. For example, in newer services being developed in New York City for children with hearing impairment, cleft palate, and epilepsy, this factor is being taken into consideration.

TABLE III. DIAGNOSTIC CLASSIFICATION AND PHYSICAL STATUS FOLLOWING SURGERY

FINAL DIAGNOSIS	TOTAL NUMBER OF CHILDREN CARED FOR IN PROGRAM	NUMBER WHO DID NOT RECEIVE SURGERY	NUMBER WHO RECEIVED SURGERY	RESULTS FOLLOWING SURGERY					
				CURED	IMPROVED	SAME	WORSE	DIED	UNKNOWN
Tetralogy of Fallot	35	6	29		21	1		7	
Patent ductus arteriosus	24	2	22	14	3	1	1	1	2
Pulmonary stenosis	15	7	8		5	1		2	
Coaretation of aorta	7	5	2		2				
Septal defect	7	7	0						
Transposition of great vessels	2	2	0						
Tricuspid atresia	2	1	1		1				
Pulmonary stenosis with patent ductus	2	1	1					1	
Aortic ring	1	0	1	1					
Coaretation with patent ductus	1	0	1	1					
Miscellaneous*	6	5	1					1	
Incomplete	27	24	3		1	2			
Total	129	60	69	16	33	5	1	12	2

*Composed of:

3 children with an assortment of multiple congenital malformations of the heart;
1 child with myxoma of the auricle;
1 child with stenosis of the aortic valve;
1 child with atrioventricularis communis.

HOW COMPLETE WAS THE SERVICE AND DID THE CHILDREN IMPROVE AS A RESULT OF THE SERVICE?

Did All Children With Potentially Remediable Lesions Have Surgery?—During the two-and-one-half-year period, 129 New York City children were cared for under the Medical Rehabilitation Program. Of this number, sixty (47 per cent) received a diagnostic work-up only, and sixty-nine (53 per cent) had the diagnostic work-up plus surgery. None of the children under the program had surgery performed for congenital heart disease without some type of diagnostic procedure being performed by the hospital doing the surgery. The final diagnostic breakdown of the 129 children cared for is shown in Table III. Of the 129 children, ninety-one (70.5 per cent) had cardiac lesions which were potentially remediable by surgery. The reasons why the sixty children did not receive surgery were varied: some lesions were not remediable (nine), the age of the child was not the most desirable one for surgery (nine), refusal of parents (two), death of the child (thirteen), movement out of the city (one), the child's condition was not such that surgery might safely be performed (twenty-three), and transfer to a nonparticipating hospital (one). In two children no known reason was found. In at least seven children whose cardiac condition was amenable to surgery, closer review and follow-up might have been of value in having surgery performed.

Type of Diagnostic Work-up.—In general, most children during the course of the diagnostic work-up received an electrocardiogram, x-ray, fluoroscopy, and hemoglobin. Angiocardiography and cardiac catheterization were performed on about one-half of the children. This pattern was true in all hospitals except Hospital 2 where there was a greater usage of angiocardiography and cardiac catheterization (Table IV). Of those children having catheterization, eleven (17 per cent) had more than one, and of those children having angiocardiography, four (7 per cent) had more than one. There was no concentration of the use of multiple procedures in any one institution. For only one child did the program pay for more than one catheterization. This again was according to policy of the program. The reason for repeat procedures was that the results of the first procedure were inconclusive. Since

TABLE IV. DIAGNOSTIC LABORATORY PROCEDURES

HOSPITAL	TOTAL NUMBER OF CHILDREN	NUMBER OF CHILDREN HAVING					
		EKG	Hgb.	X-RAY	FLUOROSCOPY	CATHETERIZATION	ANGIOCARDIOGRAPHY
1	26	26	26	26	26	8	13
2	33	33	33	33	33	30	22
3	39	38	39	39	35	13	8
4	6	6	6	6	6	0	4
5	5	5	5	5	2	4	0
6	5	5	5	4	3	3	2
7	2	2	2	2	2	1	1
8	4	4	4	3	3	1	3
Johns Hopkins	9	9	9	5	9	3	4
Total	129	128	129	123	119	63	57

staff time and materials are used at each procedure, it would seem desirable for the program to provide payment for more than one procedure on an individual child as indicated by need.

Of the sixty-three children who had at least one catheterization, forty-six (73 per cent) had it paid for by the program. Of the fifty-seven children who had at least one angiocardiogram, thirty-six (63 per cent) had it paid for by the program. The probable reason for the program's payment for a higher percentage of catheterizations is that the fee paid for them was $50, while the fee paid for angiocardiograms was $35. During the two-and-one-half-year period covered by this study, extra payment was allowed for these two major procedures, but not for such procedures as blood count, x-ray, fluoroscopy, and electrocardiogram. Hence, the program has been paying for the most expensive but least frequently used types of diagnostic procedures. Probably a sounder method of payment would be a standard average fee for diagnostic work-up which would encompass the entire block of services necessary. This might be fairer to the participating institutions and would reduce the amount of "paper work" necessary, both for the hospitals and for the program staff.

Change in Diagnosis.—Table V summarizes the data on the change in diagnosis of the group as a result of the diagnostic work-up, surgery, and autopsy. The percentage of children with a change in diagnosis after diagnostic work-up was 36 per cent and after autopsy was 45 per cent. These data point out that an accurate diagnosis of children with congenital heart disease is by no means simple even with the liberal definition used for change in diagnosis. These facts would seem to substantiate the need for concentrating the patients in fewer hospitals to enlarge the experience and skill of the hospital staffs within the community.

TABLE V. CHANGE IN DIAGNOSIS

DIAGNOSIS STATUS	NUMBER OF CHILDREN
1. *After Diagnostic Work-up*	129 (100%)
Remained same as pre-work-up diagnosis	82
Diagnosis changed*	46 (36%)
Unknown	1
2. *After Surgery*	69 (100%)
Remained same as diagnostic work-up diagnosis	61
Diagnosis changed*	5 (7%)
No diagnosis reached	3
3. *After Autopsy*	
A. *Surgical Group*	12 (100%)
Remained same as diagnosis after surgery	9
Diagnosis changed*	3 (25%)
B. *Nonsurgical Group*	10 (100%)
Remained same as diagnostic work-up diagnosis	3
Diagnosis changed*	7 (70%)

*Diagnosis changed is defined as any case in which the major diagnosis did not remain the same and in which the change in diagnosis would have influenced the management of the child.

Result to the Child.—Of the sixty-nine children having surgery for congenital heart disease, sixteen (23 per cent) were cured and thirty-three (48 per cent) were improved. Five children (7 per cent) remained the same after surgery, and one child was worse. Twelve children (17 per cent) died. Thus, some degree of improvement was provided for 71 per cent of the children receiving surgery. This information is based on hospital follow-up over a postoperative period varying from several months to more than two years. Criteria used in this evaluation included such symptoms as

dyspnea, cyanosis, clubbing, fatigability, difficulty in feeding, attacks of unconsciousness, frequent respiratory infections, amount of activity, and such signs as heart size, murmurs, and blood pressure (Table III).

Of the 129 children cared for under the program, twenty-three (18 per cent) died, of whom twelve were in the operated group and eleven in the nonoperated group. The largest single diagnostic group in which death occurred was that of tetralogy of Fallot, in which seven of thirty-five died. Eleven deaths occurred in children who had multiple congenital malformations of the heart. The remaining five deaths occurred in a scattering of individual anomalies, most of which were of a serious nature (transposition of the great vessels, patent atrioventricularis communis, stenosis of aortic valve, and pulmonary stenosis).

Change in School Placement.—One important aspect of the rehabilitation of children with congenital heart disease would be to show the extent of improvement as illustrated by school placement before and after the diagnostic work-up and surgery. Unfortunately, the data on both the hospital records and within the program were too incomplete to demonstrate any clear pattern.

WHAT ARE THE COSTS AND WHAT WAS THE LENGTH OF HOSPITAL STAY?

Payment for Service.—A total of $26,415.74 was paid by the program for the care of 121 children. In the other eight cases final requests for payment have not been received. This is an average of $218.31 per child. The amount expended for children with congenital heart disease during this two-and-one-half-year period represents 1 per cent of the total expenditure in the New York City medical rehabilitation program. Of the total expenditure, $19,054.27 (72 per cent) was spent for the group that had diagnostic work-up plus surgery. The average cost of the operated group ($293) was more than twice that of the nonoperated group ($131). As would be expected, hospital care was the largest single item of service paid for, accounting for 76 per cent of total expenditures, with catheterization, special nursing, and angiocardiography running next in amount of expenditure. The operated group had a proportionately larger share of its funds spent for hospital care and special nursing, while the nonoperated group had a proportionately larger share spent for catheterization and angiocardiography (Table VI).

A comparison of expenditures of the survival and death groups reveals a much higher average cost per case in the death group. The group of patients who died had a larger percentage of its funds expended for special nursing and for special services such as drugs, blood, and oxygen (Table VI).

This amount of payment by the program for the care of these children does not represent total payments, as it does not include any information on the amounts paid by the families and by other sources such as prepaid insurance.

Length of Stay.—Table VII shows the data on length of hospital stay. For the total group of 105 children, where there was complete information, the average length of hospital stay

TABLE VI. PAYMENT FOR CARE OF CHILDREN WITH CONGENITAL HEART DISEASE

	TOTAL HEALTH DEPARTMENT PAYMENT		BY TYPE OF SERVICE				BY OUTCOME			
			OPERATED GROUP		NONOPERATED GROUP		SURVIVAL		DEATHS	
	AMOUNT	PER CENT	AMOUNT	PER CENT	AMOUNT	PER CENT	AMOUNT	PER CENT	AMOUNT	PER CENT
Hospital care	$20,165.14	76.3	$15,241.41	80.0	$4,923.73	66.9	$16,055.31	76.4	$4,109.83	76.2
Catheterization	1,800.00	6.8	500.00	2.6	1,300.00	17.7	1,600.00	7.6	200.00	3.7
Special nursing	1,416.00	5.4	1,416.00	7.4	—	—	903.00	4.3	513.00	9.5
Angiocardiography	1,039.00	3.9	304.00	1.6	735.00	10.0	920.00	4.4	119.00	2.2
Physicians' fees	640.00	2.4	640.00	3.4	—	—	640.00	3.0	—	—
Drugs, blood, oxygen	541.60	2.1	377.52	2.0	164.08	2.2	319.80	1.5	221.80	4.1
Operating room and anesthesia	370.00	1.4	300.0	1.6	70.00	0.9	295.00	1.4	75.00	1.4
Laboratory	347.50	1.3	275.34	1.4	72.16	1.0	289.50	1.4	58.00	1.1
Other*	96.50	0.4	—	—	96.50	1.3	—	—	96.50	1.8
Total	$26,415.74	100.0	$19,054.27	100.0	$7,361.47	100.0	$21,022.61	100.0	$5,393.13	100.0
Number of children with complete invoices	121		65		56		102		19	
Average cost per child	$218.31		$293.14		$131.45		$206.10		$283.85	

*For one wheel chair for one patient.

was 31.9 days, of which 16.6 days (52 per cent) were covered by the program. Of the total group of 105 children, the program paid for the entire hospital care of only thirty-six (34 per cent). The average length of hospital stay in the operated group was more than twice that of the nonoperated group. The operated group had a higher percentage of hospital days covered by the program than did the nonoperated group. One of the important facts shown by Table VII is that this program, which is intended for the diagnosis, treatment, and rehabilitation of children with congenital heart disease, has not only been limited in the number of children covered but also has been limited in the extent of care which has been afforded to the children whom the program has reached. This has been directly related to the policy of not including payment for the medical care of the child during the period of hospital stay, for example, the child with congenital heart disease who is decompensated and who requires a period of medical care and treatment, prior to the performance of diagnostic work-up or surgery. It would seem desirable to revise this policy, particularly since many of the participating hospitals have felt that it was medically unwise from the viewpoint of the care of the child.

TABLE VII. LENGTH OF HOSPITAL STAY

	TOTAL	BY SERVICE		BY OUTCOME	
		OPERATED GROUP*	NON-OPERATED GROUP†	SURVIVAL‡	DEATHS§
Total number of children with complete data	105	57	48	90	15
Total hospital days	3,347	2,424	923	2,739	608
Average length of stay: Total hospital days	31.9	42.5	19.2	30.4	40.5
Total hospital days covered by Health Department program	1,749	1,415	334	1,369	380
Average length of stay: Total hospital days covered by Health Department program	16.7	24.8	7.0	15.2	25.3
Per cent of total hospital days by Health Department program	52.3	58.4	36.2	50.0	62.5

*Of the 57 children, the Health Department paid for all hospital days of 19.
†Of the 48 children, the Health Department paid for all hospital days of 17.
‡Of the 90 children, the Health Department paid for all hospital days of 34.
§Of the 15 children, the Health Department paid for all hospital days of 2.

The length of stay and extent of coverage by the program were greater in the group of patients who died than in the group of patients who survived.

Further analysis of length of stay was undertaken by individual hospitals participating in the program. The number of patients per individual hospital is small so that it is not possible to demonstrate any statistically significant difference among the participating hospitals.

DISCUSSION

In order to test the effectiveness of services to the public, it is necessary to analyze programs. This study of children with congenital heart disease is the first analysis to be undertaken in the New York City medical rehabilitation program and obviously should now be extended to include other kinds of handicapped children cared for under this program.

The administrative leads which have resulted from this analysis are: (1) there should be wider dissemination about the program to the professional groups and to the public; (2) current cost of living data should be used in determining financial eligibility in a medical care program; (3) purchase of care for patients should be made on a cost basis; (4) effort should be made to improve case-finding in the adolescent and teen-age group; (5) the entire question of the number of hospitals participating in this program should be reviewed with the Cardiac Surgery Advisory Committee; (6) a combined plan for closer review and follow-up by the individual hospital and the Bureau for Handicapped Children in New York City should be instituted to see what assistance may be given to the family having a child with congenital heart disease remediable by surgery who has not yet had surgery performed; obviously this type of assistance should really come primarily from the staff of the individual institution, but supplementary assistance from public health resources may be helpful to the family; (7) program policies which should be reviewed and revised should include (a) payment for only one angiocardiogram and for only one catheterization per child, (b) exclusion of payment for the purely conservative inpatient medical care of children with congenital heart disease, and (c) payment for patient care on a piecemeal basis instead of a standard average fee for certain blocks of total service; (8) improvement should be made in the school placement program so that placement is optimal for the child and more adequate information will be available on handicapped children; (9) broader knowledge should be gained of the incidence and prevalence of handicapping conditions; (10) knowledge of total cost of care for handicapped children should be acquired.

Although at present we do not have the specific facts to prove that the weaknesses found in the congenital heart disease aspect of the medical rehabilitation program apply equally well to the services for other kinds of handicapped children, nevertheless it is our general impression that many of them are applicable. Similar steps of major importance should be taken in the services for other kinds of handicapped children while additional studies of these groups are being performed.

This study of children with congenital heart disease does not include any data on the quality of service being given by the participating institutions. When the revision of the standards for hospital care is completed, it is planned to conduct surveys of the participating institutions. These surveys will be conducted by a team composed of a cardiologist, pediatrician, hospital nursing consultant, and medical social worker. Most of the institutions participating in the orthopedic program of the Bureau for Handicapped Children have now been surveyed.

The results of such surveys indicate the need for improvement in patient care, and this may be true for other types of handicapped children.

SUMMARY

A study of the first 129 children with congenital heart disease cared for in the New York City medical rehabilitation program reveals the following facts:

1. This group of 129 children represents 41 per cent of the children with congenital heart disease cared for by the participating hospitals during the period studied.

2. Most of the children were in the infant, preschool, and early school-age groups.

3. Three of the nine participating hospitals cared for 76 per cent of the children in the program.

4. Forty-seven per cent of the children received a diagnostic work-up only, and 53 per cent received a diagnostic work-up and surgery.

5. At each step of the way in the management of children with congenital heart disease, a considerable number of children had a change in diagnosis.

6. Of the children having surgery, 23 per cent were cured and 48 per cent were improved. Seventeen per cent of the children died during or after surgery.

7. The average cost per child was $218.31.

8. The average length of hospital stay was 31.9 days, of which 16.7 days were covered by the program.

The implications of these findings for improvement in the administration of the program and in the care of handicapped children are discussed.

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TETRACYCLINE: STUDIES ON ABSORPTION, DISTRIBUTION, EXCRETION, AND CLINICAL TRIAL IN CHILDREN

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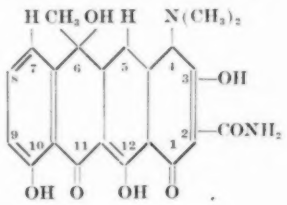
TETRACYCLINE is a new broad-spectrum antibiotic which may be prepared by catalytic dechlorination of chlortetracycline (Aureomycin)[1, 2] or by fermentation.[3]

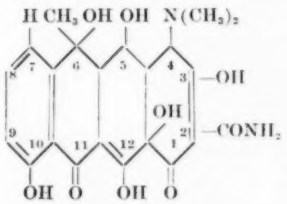
It was first reported by Stephens[4] in 1952 that the chemical moiety designated as tetracycline was common to the broad-spectrum antibiotics oxytetracycline and chlortetracycline.

The differences in chemical structure of these compounds is clearly apparent. Tetracyn is the parent substance of this group of antibiotics. It has hydrogen atoms attached to the two carbon atoms designated as No. 5 and No. 7. On the other hand, Terramycin has at these positions hydroxyl and hydrogen, respectively. Aureomycin, while having a hydrogen attached to the No. 5 carbon atom, has a chlorine at the No. 7 carbon atom.

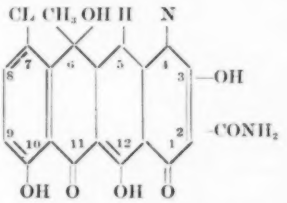
The antibiotic Tetracyn* has the following molecular structure:



Terramycin's* structure is:



Aureomycin† has a structure represented as follows:



Tetracyn, an amphoteric compound, has been shown to have a low degree of toxicity in experimental animals.[5] As determined by English and associates,[6] the magnitude of sensitivity of bacteria to tetracycline is very similar to oxytetracycline and chlortetracycline. The behavior of resistant cultures is also parallel. All gram-positive microorganisms (with the exception of Corynebacterium species) were sensitive to tetracycline in vitro in a concentration range of 0.312 to 1.56 μg per milliliter and gram-negative ones

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*The antibiotic used in this study was Tetracyn brand of tetracycline supplied by the Medical Research Department of J. B. Roerig & Co.

*Trademark of Chas. Pfizer & Co., Inc., for oxytetracycline.

†Trademark of American Cyanamid Co., for chlortetracycline.

in a concentration range of 0.39 to 3.12 μg per milliliter. Tetracycline showed no activity against our strains of Bacillus Proteus and only limited activity against the cultures of Pseudomonas aeruginosa used in this study. The action of the antibiotic is definitely bacteriostatic, but bactericidal action can be elicited. According to English and co-workers[6] a range of four to seventy times the bacteriostatic concentration was necessary to produce a bactericidal action with gram-negative bacteria, and about three to thirty-three times for the various gram-positive microorganisms.

The preliminary reports were encouraging. Our study in infants and children was undertaken to determine (1) the rapidity of absorption from the gastrointestinal tract, (2) duration of serum levels after single and multiple oral doses in various age groups, placed on different dosage schedules, (3) diffusibility into the cerebrospinal fluid, (4) urinary excretion, (5) tolerance, (6) therapeutic effect, and (7) to establish a rational dosage schedule for children.

TABLE I. SERUM TETRACYCLINE LEVELS AFTER A SINGLE ORAL DOSE

DOSE MG./KG.	PATIENT	AGE	DOSE (MG.)	SERUM LEVELS, μG/ML. HOURS AFTER DOSAGE 2	8	12
3	1	8 yr.	85	*0.625	** 0	—
	2	15 mo.	30	*0.312	** 0	—
	3	3½ yr.	50	*0.312	** 0	—
	4	5 yr.	60	0.312	0	—
	5	11 yr.	120	*0.312	** 0	—
Mean level				0.374	0	
6	1	10 yr.	220	1.250	0.625	—
	2	15 mo.	60	0.625	0.625	—
	3	7 yr.	145	0.625	0.312	—
	4	8 yr.	170	0.625	0.312	—
	5	11 yr.	240	0.312	0.312	—
Mean level				0.687	0.437	
12.5	1	10 yr.	450	2.500	0.625	0.312
	2	1 mo.	40	1.250	0.625	—
	3	10 yr.	400	1.250	0.625	—
	4	13 yr.	500	1.250	1.250	0.625
	5	3 yr.	200	0.625	0.625	0.312
Mean level				1.374	0.740	0.416
25	1	6 mo.	175	5.000	1.250	1.250
	2	17 mo.	275	5.000	1.250	0.312
	3	3 yr.	300	2.500	0.625	—
	4	16 mo.	325	1.250	5.000	—
	5	9 yr.	700	1.250	0.625	0.312
Mean level				3.000	1.750	0.623
50	1	9 mo.	400	10.000	2.500	1.250
	2	19 mo.	700	10.000	1.250	—
	3	10 yr.	1650	5.000	2.500	1.250
	4	7 yr.	1400	2.500	10.000	2.500
	5	15 mo.	600	2.500	2.500	—
Mean level				6.000	3.750	1.666

*One-hour serum level.
**Six-hour serum level.

METHODS

The drug was administered orally in the form of chocolate suspension,

in a concentration of 50 mg. per cubic centimeter. The children used in this pharmacological study, forty-four in number, ranging in age from 1 month to 13 years, were hospitalized patients convalescing from various diseases, all free from any evidence suggesting impairment of renal or cardiac function. During the procedures, no restriction of diet was ordered. The single tetracycline dose was given one-half or one hour after breakfast.

RESULTS

A. *Pharmacological Data.*—

1. The absorption of tetracycline from the gastrointestinal tract was rapid. A concentration of 1.25 μg per milliliter of serum was detected within one-half hour after 50 mg. per kilogram dose, and 0.625 μg per milliliter after administration of 25 mg. per kilogram dose. No antibiotic activity was detected in children who

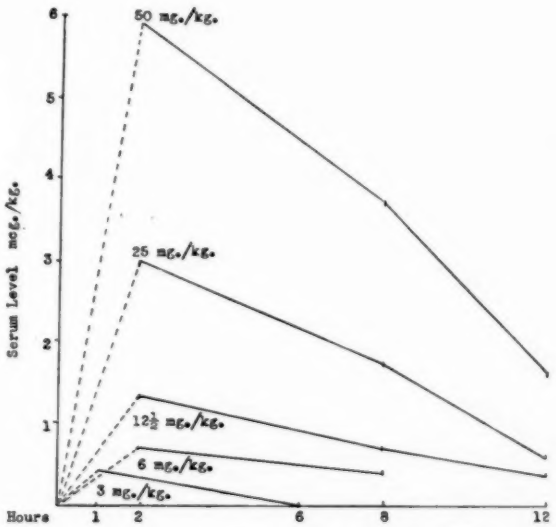

Fig. 1.—Tetracycline mean serum levels after varying dosages.

Blood specimens were allowed to clot for twenty minutes; the serum was separated and stored at 0° F. Cerebrospinal fluid and urine specimens were stored immediately at 0° F. Body fluid tetracycline levels were determined within six to twenty-four hours at the Research Laboratories of Chas. Pfizer & Co., Inc., by the modified twofold dilution technique as described by English and associates.[7]

received 12.5 and 6 mg. per kilogram dose in thirty minutes after dose was given.

2. Serum levels. To determine the duration of serum level produced by a single oral dose, five groups of five children each were given 3, 6, 12½, 25, and 50 mg. per kilogram dose. The results obtained are given in Table I.

It is noted that the dose of 3 mg. per kilogram produced serum levels

only at one- or two-hour intervals. By increasing the dose to 6 mg. the two-hour mean serum level was 0.68 μg per milliliter. After eight hours a mean value of 0.43 μg was obtained. In five patients who received 12½ mg. dose, the range of the two-hour level was 2.5 to 0.625 μg, with a mean of 1.375 μg. After eight hours the mean level was 0.75 μg, and at twelve hours 0.41 μg. By increasing the dose to the two-hour level exceeded the eight-hour; in five patients the values were equal.

A summation of the mean serum levels, on the five single doses, is shown graphically in Fig. 1.

3. Cumulation. In order to determine the effect of cumulation, a group of nine patients was given tetracycline every six or eight hours for two days. The blood samples were obtained on

TABLE II. SERUM TETRACYCLINE LEVELS AFTER MULTIPLE ORAL DOSAGES

DOSE	PATIENT	AGE	SERUM LEVEL μG/ML.			
			FIRST DAY		SECOND DAY	
			2-HOUR	6-HOUR	2-HOUR	6-HOUR
3 mg./kg. every 6 hr.	1	4 yr.	0.312	0	1.250	0.625
	2	7 yr.	0.625	0	0.312	0.625
	3	8 yr.	0.312	0	0.625	0.312
Mean level			0.416	0	0.729	0.654
6 mg./kg. every 6 hr.	1	7 yr.	0.625	0.625	0.625	1.250
	2	12 yr.	2.500	0.625	2.500	2.500
	3	8 yr.	0.625	0.625	2.500	2.500
Mean level			1.250	0.625	1.875	2.050
6 mg./kg. every 8 hr.	1	3 yr.	2.500	*0.312	1.250	*1.250
	2	7 yr.	0.625	*0.625	1.250	*1.250
	3	5 yr.	0.625	*0.625	0.625	*0.625
Mean level			1.250	0.654	1.042	1.042

*Eight-hour serum level.

TABLE III. SERUM AND SPINAL FLUID LEVELS AFTER ONE DAY OF THERAPY. SAMPLES OBTAINED SIX HOURS AFTER FINAL DOSE.

DOSE	PATIENT	AGE	μG./ML., 6 HR. AFTER LAST DOSE	
			SERUM	CEREBROSPINAL FLUID
25 mg./kg. every 6 hr.	1	10 mo.	10.000	1.250
	2	16 mo.	2.500	0
35 mg./kg. every 6 hr.	1	7 yr.	10.000	0.312
	2	4½ yr.	5.000	0.625

25 mg., the two-hour level ranged between 5.0 and 1.25 μg; eight hours, between 5.0 and 0.625 μg; twelve hours, between 1.25 and 0.312 μg. The mean values were 3.0, 1.75, and 0.63 μg, respectively. In patients who received the 50 mg. dose the mean serum levels were further increased to 6.0 μg at two hours, 3.75 μg, at eight hours, and 1.6 μg at twelve hours. In all patients, except two, two consecutive days, two and six or eight hours after the 8:00 A.M. dose.

As shown in Table II and Fig. 2, patients who received the dose of 3 mg. per kilogram every six hours showed appreciable serum levels in the second day of treatment. A tendency toward cumulation was observed only in two patients who received a 6 mg. dose every eight hours. A marked cumulative effect was ob-

tained in two patients who received a 6 mg. dose, but at six-hour intervals. Their two- and six-hour levels were four times higher than on the first day.

4. Diffusion into the cerebrospinal fluid. Two patients received a dose of 25 mg. and two 35 mg. at six-hour intervals for one day. Blood and spinal fluid were obtained six hours after the last dose. All patients were free of meningeal inflammation.

The results shown in Table III do not indicate definite correlation with serum levels.

5. Urinary excretion. Fig. 3 shows the pattern of tetracycline excretion in the urine.

Twenty-five milligrams per kilogram dose (700 mg.) was given to a 7-year-old patient and 12.5 mg. per kilogram (460 mg.) to an 11-year-old patient. Urine samples were collected one, three, six, nine, twelve, twenty and

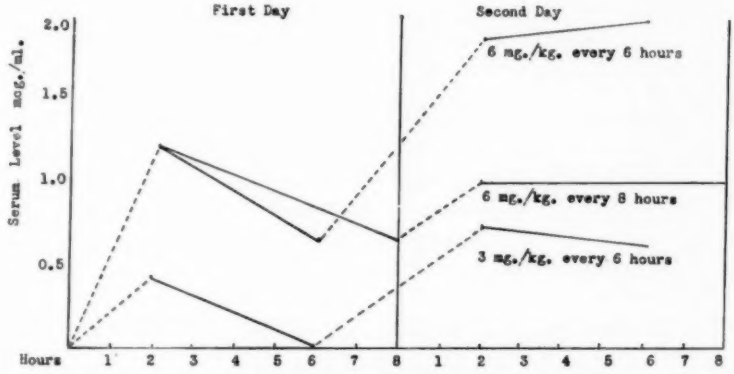

Fig. 2.—Tetracycline mean serum levels after varying multiple dosages.

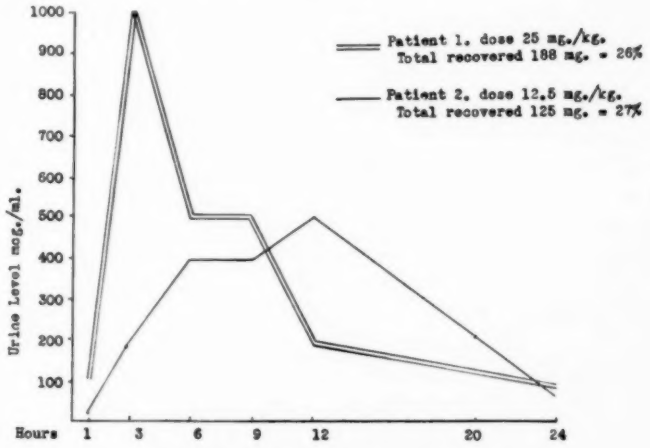

Fig. 3.—Urine tetracycline levels after single oral dose.

twenty-four hours later. The urinary excretion began one hour after dosing, the maximum excretory rate occurred between the third and sixth hours, and twenty-six per cent (patient 1) and 27 per cent (patient 2) of the total amount given was recovered within twenty-four hours.

B. *Clinical Results.*—

1. Tolerance. The drug was given to seventy-three patients ranging in age between 1 month and 13 years, in doses of 12.5 to 150 mg. per kilogram per day orally in courses lasting up to two weeks. Vomiting occurred in three children on only one occasion, but it is questionable whether it was related to the antibiotic. A mild maculopapular rash was noticed in one child, which disappeared two days after the drug was discontinued.

2. Therapeutic effect. A group of fifty-one hospitalized patients with various infections were treated with oral tetracycline in a dose of 12½ to 25 mg. per kilogram per day. The results are presented in Table IV.

Table IV. Therapeutic Effect in Fifty-one Patients Treated With Oral Tetracycline

Clinical diagnosis	Number of patients treated	Average duration of treatment in days	Result			
			Cured	Improved	Not improved	Recurrence
Nasopharyngitis	8	4.0	6	1		1
Acute tonsillitis	7	3.2	7			
Acute otitis media	5	3.8	4			1
Acute laryngotracheobronchitis	3	5.2	2	1		
Acute and chronic bronchitis	16	6.3	13	1	1	1
Bronchopneumonia	5	6.0	5			
Lobar pneumonia	1	6.0	1			
Acute conjunctivitis	1	4.5	1			
Cellulitis	2	5.0	1	1		
Impetigo	1	4.0	1			
Acute lymphadenitis	2	4.0	2			

in all cases. In twenty-nine patients the dose was 25 mg. per kilogram per day, divided into three equal doses; in six patients 25 mg. per kilogram per day divided into four doses, and in sixteen patients, 12.5 mg. into four doses. Of fifty-one patients, forty-three (84.5 per cent) were cured, four (7.8 per cent) improved, and one (1.9 per cent) not improved. In three patients the symptoms recurred within one or two days after the treatment was discontinued. Two of them received a 12.5 mg. per kilogram per day dose. Tetracycline resistant staphylococci was recovered in three cases at the beginning of treatment. In another case, the organism (hemolytic *Staphylococcus aureus*) developed resistance to tetracycline during the course of treatment. These are recorded in Table IV as "unimproved" and "recurrences." Erythromycin was the effective therapeutic agent in these cases.

A striking feature observed was rapid defervescence. In 41 per cent of the cases, the temperature was normal within twelve hours; in 22 per cent, in twenty-four hours; and in 29 per cent the patients became afebrile after more than one day of therapy.

Bacteriological studies were performed on all patients, but predominating organisms (streptococci, staphylococci, pneumococci, and *Hemophilus influenzae*) were not identified

Six per cent of the patients were afebrile at the start of treatment.

DISCUSSION

The study presented shows that tetracycline is absorbed rapidly from the gastrointestinal tract and produces appreciable serum levels.

Antibiotic activity was detected in serum within one-half hour after the administration of 25 and 50 mg. per kilogram doses.

The smallest tetracycline oral dose which produced a therapeutic serum level of eight-hour duration was 6 mg. per kilogram; an increase of the dose resulted in proportionate increase of the mean serum levels. The highest concentration, 10 μg per milliliter, was reached after the administration of a 50 mg. per kilogram dose.

The pattern of absorption of tetracycline in children seems to be different from that of oxytetracycline[8] and chlortetracycline.[9] These are absorbed more slowly. There appears to be a limiting factor in absorption so that increasing the dosage above a certain point does not produce an increased serum level. In respect to the pattern of absorption, tetracycline is quite similar to chloramphenicol.[10, 11]

Of great importance is the marked cumulative effect which is produced when tetracycline is given in doses of 3 or 6 mg. per kilogram every six hours. Less cumulation was demonstrated when a 6 mg. per kilogram dose was given in an eight-hour interval.

Tetracycline penetrates the cerebrospinal fluid barrier poorly in patients without meningeal inflammation. The cerebrospinal fluid level ranged from one-eighth to one-thirtieth of the simultaneous serum level, which resembles the pattern of oxytetracycline[8] and chlortetracycline,[9] but is in sharp contrast to chloramphenicol.[10]

Tetracycline is excreted in high concentrations in the urine (up to 1,000 μg per milliliter). The urinary excretion over a twenty-four-hour period was 26.5 per cent of the total dose, higher than that of oxytetracycline and chlortetracycline, but lower than that of chloramphenicol.[11] The excretion began within one hour, and the maximum excretory rate occurred between three and six hours.

The studies presented indicate that tetracycline, given orally in doses of 25 mg. per kilogram per day, divided into three or four equal dosages, produces a serum concentration equal to or greater than the in vitro minimal inhibitory concentrations for the majority of susceptible organisms.[6]

Data on the rapidity of tetracycline diffusibility into the cerebrospinal fluid are lacking because the earliest assays were performed after twenty-four-hour therapy. Intravenous[12] or intramuscular[13] administration of the initial dose, therefore, would seem to be necessary in treatment of meningitis.

Tetracycline doses up to 150 mg. per kilogram per day have been exceptionally well tolerated. The lack of side reactions, the palatability of the suspension, allowing easy administration to children, and its efficacy in infectious diseases, are sufficient to warrant further investigation to elucidate the final place of this new antibiotic in the treatment of children.

SUMMARY

1. Tetracycline is absorbed rapidly into the blood stream after oral administration. Antibiotic activity was detected one-half hour after 25 and 50 mg. per kilogram doses.

2. Therapeutic serum levels of eight hours' duration were produced with a single 6 mg. per kilogram dose. Further increase of dosage produced a proportional increase of serum concentration.

3. A marked cumulative effect was obtained by the second day of therapy, when the dose of 3 and 6 mg. per kilogram was given at six-hour intervals, thereby providing more effective blood levels.

4. Tetracycline diffuses poorly into the cerebrospinal fluid in patients without meningeal inflammation. The spinal fluid level ranged from one-eighth to one-thirtieth of the simultaneously obtained serum levels.

5. Tetracycline is excreted in high concentrations up to 1,000 μg per milliliter in the urine. The total excretion over a twenty-four-hour period was 26.5 of the given dose.

6. Patients show a high tolerance to the drug. A remarkable lack of side reactions was observed even with a dose of 150 mg. per kilogram per day.

7. Of fifty-one patients treated with the oral suspension, 84.5 per cent were cured, 7.8 per cent improved, and 1.9 per cent unimproved. There were three (5.8 per cent) recrudescences.

8. The studies indicate that the effective oral dose of tetracycline is 25 mg. per kilogram per day given at six- to eight-hour intervals.

We wish to thank Dr. A. English of the Chas. Pfizer & Co., Inc., for his assistance.

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COMBINED DRUG THERAPY IN PETIT MAL EPILEPSY

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IN RECENT years a considerable number of new anticonvulsant drugs have become available both in the pharmacopeia and for investigation. Most of these have been advocated for use in the control of major seizures (i.e., grand mal, psychomotor) and have proved inadequate in the control of petit mal epilepsy. In 1945 Lennox first reported on the use of a new drug, Tridione (3,5,5-trimethyloxazolidine-2,4-dione), in the petit mal epilepsies. Since then it has been considered that this drug is the most effective thus far available in the treatment of this condition. However, it has the disadvantage of being toxic to the hematopoietic system upon prolonged use, as well as having other less severe side effects.

In 1951 another compound, Milontin (N-methyl-α-phenylsuccinimide),* was introduced for clinical investigation. In 1951 Zimmerman[1] reported the use of Milontin on fifty patients with petit mal epilepsy. He concluded that Milontin equaled or surpassed Tridione in therapeutic efficacy and had the advantage of being relatively nontoxic.

Millichap[2] in London reported on the use of Milontin among twenty cases in 1952. His studies also produced similar results although he encountered more toxic effects than reported by Zimmerman.

Doyle and associates[4] in August, 1953, reported the use of Milontin in twenty-one patients, with simple absence seizures associated with 3 per second spike and wave pattern in electroencephalogram. They reported that not one of these patients responded to this medication in the dosages employed.

The following is a report of our experience in the use of this new drug alone and more particularly in combination with Tridione.

CLASSIFICATION OF CLINICAL MATERIAL

In our series there were fifteen patients with petit mal seizures. These were classified as follows:

1. Idiopathic petit mal triad.
   (a) Absence (pyknolepsy)—manifested by transient loss of consciousness with no motor component.
   (b) Akinetic—transient loss of consciousness accompanied by loss of postural tone.
   (c) Myoclonic—minor transient motor phenomena involving one or more muscle groups.
2. Symptomatic seizures manifested by one or more of the petit mal triad pattern.
3. Mixed petit mal—petit mal combined with grand mal seizures.

CASE MATERIAL

We recognize that fifteen patients constitute a small series, but it is believed that some of our observations warrant reporting at this time. The cases were selected from a large group

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*We are indebted to Dr. H. E. Carnes of Parke, Davis & Company for our supply of Milontin.

of children between the ages of 2 and 15 years in the Blue Bird Children's Clinic for Neurological Disorders and the consultation practice of one of us (W. S. F.). Eleven were clinic and four were private patients. All clinical diagnoses were correlated with electroencephalographic data. Eleven of these patients had been previously tried on other medication as follows:

	Number of Cases
Phenobarbital	6
Tridione	5
Mebaral	4
Dilantin	4
Dexedrine	3
Gemonil	2
Paradione	2
Glutamic acid	1

We have selected cases in which the control of seizures was far from adequate. Other patients with petit mal seizures in our clinic group who were already adequately controlled on other medication were not included in this study. There were nine cases of idiopathic petit mal, four cases of symptomatic seizures with petit mal pattern and two of mixed petit mal.

Of the nine cases of idiopathic petit mal, seven had absence seizures alone, one had akinetic and myoclonic seizures, and one had the entire triad of seizures. All of these patients were having more than twenty seizures daily and two were in petit mal *status epilepticus* when first seen. Each was started on Milontin 0.5 Gm. three times daily and the dosage increased after one week to 1.0 Gm. three times daily. Once this dosage was reached, all of these patients showed reduction in the frequency of their attacks and three were seizure-free for from four to five weeks. In each instance, however, after periods varying from four to twelve weeks, the number of seizures began to increase or toxic effects became manifest. In six of the patients, Tridione 0.3 Gm. t.i.d. was added to the Milontin while the dose of the latter was decreased to 0.5 Gm. t.i.d. Two were changed to Tridione alone because of marked urinary frequency and urgency which was felt to be attributable to Milontin. Another was changed to Tridione alone because of severe drowsiness and poor control of seizures on Milontin alone. One patient with absence seizures developed gross hematuria when the total dose of Milontin reached 3.0 Gm. This was followed by microscopic hematuria until the dose was reduced to 1.5 Gm. daily. After reducing the medication, more seizures were noted. When Tridione 0.9 Gm. daily was added, complete control was achieved except when the child was exposed to bright, flickering sunlight. This was surprising in view of the complete failure of Tridione previously, without Milontin. There were, in addition, three others in this group who are now seizure-free on the combined drug therapy who had failed previously to respond to Tridione alone.

Of the four with symptomatic seizures, all had more than one manifestation of the petit mal triad as well as other types of seizures. The electroencephalogram in each showed diffuse slow spike wave dysrhythmia, which was considered suggestive of the existence of a symptomatic convulsive state. Milontin in a dose of 3.0 Gm. daily completely controlled only one of these patients. Two others still have one to three seizures daily on Milontin 1.5 Gm. together with other medication. One of these developed hematuria on a dose of 3.0 Gm. daily. The fourth

patient, who has a postencephalitic convulsive disorder, developed severe anorexia on Milontin 1.5 Gm. daily and the medication had to be discontinued and replaced by Tridione and phenobarbital.

Two patients had idiopathic petit mal combined with grand mal seizures. Both are well controlled on Milontin 3.0 Gm. with Mebaral 0.2 Gm. daily. One has been seizure-free for seven months and the other, a 12-year-old girl, has had only one or two attacks during menstruation over a period of seventeen months.

The length of treatment of these fifteen patients varied from seven to twenty-one months.

DISCUSSION

The results in this series of patients suggest that Milontin is effective in the treatment of idiopathic petit mal seizures. The best results in this group were achieved when Milontin 0.5 Gm. was combined with Tridione 0.3 Gm. three times daily. With the seven patients on this regime, 100 per cent control of seizures was achieved. This was remarkable in several instances where the patients had not been adequately controlled previously by either one of these drugs independently.

Milontin in combination with Mebaral was very useful in controlling idiopathic seizures when both minor and major attacks were present. Major attacks were not exacerbated by the introduction of Milontin. The results in the patients in whom the petit mal type of seizures were of symptomatic origin have been the least satisfactory.

Toxic Manifestations.—The toxic manifestations of Tridione are well documented but those of Milontin are still under investigation. Miller and Long[3] reported that Milontin was well tolerated in laboratory animals and was effective in the control of Metrazol-induced seizures.

In Zimmerman's series of fifty patients, toxic reactions occurred in 22 per cent and the symptoms were: nausea, dizziness, drowsiness, vomiting, and headache.

In Millichap's twenty patients, 62 per cent exhibited toxic effects which included: abnormal urinary findings (10), drowsiness (5), nausea (4), dreamlike state (3), dizziness (2), erythema multiforme (1), vomiting (1).

Doyle and associates[4] found no toxic reaction in the twenty-one cases they studied. Eight of these patients had monthly urinalyses but no hematuria was encountered.

All of our patients have had complete blood studies at least once a month and no abnormality has been encountered. In addition, urinalysis has been made at the same time as each blood examination. Two patients developed hematuria and one of these also had urinary frequency. Two other patients had frequency and urgency of urination without hematuria. Two patients developed enuresis. In all of these patients urinary symptoms disappeared when the dosage of the drug was reduced. One patient developed anorexia sufficiently severe to necessitate discontinuing Milontin therapy. Another patient developed a dreamlike state for a few hours every day. In this instance, Milontin was also discontinued.

Our observation agrees with that of Millichap, that urinary symptoms are the most frequent toxic manifestations when larger doses of Milontin (3.0 Gm. or over, daily) are employed. However, five of Millichap's patients

had microscopic hematuria on a dosage as low as 0.9 Gm. daily. None of our patients developed toxic symptoms on this small a dose. Nothing is known about the pathological basis of the hematuria. The presence of bladder symptoms and the absence of other abnormal urinary findings would seem to indicate that it is an irritative phenomenon.

Parents of three patients observed that the medication must be given promptly, according to the prescribed schedule, or seizures would occur. This suggests that there is no cumulative effect of this drug. The effective blood level can be maintained for only about four to five hours following an oral dose of Milontin.

SUMMARY

1. The therapeutic efficacy and toxic manifestations of Milontin were investigated in a series of fifteen patients with petit mal epilepsy.

2. Milontin alone, when employed in sufficiently large doses, controlled only three of the patients without toxic effects.

3. Milontin in smaller doses, combined with Tridione, was more effective in the control of seizures in seven patients than either drug independently.

4. Because of toxic manifestations, Milontin was reduced in dosage in six patients and completely discontinued in three patients.

5. Milontin does not appear to have greater benefit in the control of petit mal seizures when used alone than drugs previously available. However, it is more effective when used in combination with Tridione.

6. The toxic manifestations of this combined drug therapy are no greater than those of either drug used independently.

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ORAL CALCIUM EDTA IN LEAD INTOXICATION OF CHILDREN

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THE use of disodium calcium ethylenediaminetetraacetate (CaEDTA), an organic chelating agent, has been reported in the treatment of lead intoxication.[1, 2, 3] The ability of the agent to chelate lead, the ready excretion of water-soluble chelates and the absence of toxic effects because of the nonionizable stable complex formed with lead prompted the use of CaEDTA in this field.

Sidbury and associates[4] first reported the use of oral CaEDTA in lead intoxication. These workers administered the drug to a total of seven patients, two of whom were children. Intravenous and oral methods of administration to the children were used alternately during the same course of treatment. Their results indicated that oral CaEDTA produced a five- to tenfold increase in twenty-four-hour urinary lead excretion with maximum excretion occurring on the third or fourth day. Intravenous CaEDTA, however, produced a ten- to fortyfold increase in urinary lead excretion with maximal excretion being reached in the first twenty-four hours following administration.

The present study reports the effect of oral CaEDTA* used alone on five cases of chronic lead intoxication in children.

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*The oral disodium calcium ethylenediaminetetraacetate was supplied by Riker Laboratories, Inc., Los Angeles, Calif.

METHODS

Children with a documented history of eating paint and/or plaster of a toxic lead content were selected from the Developmental Clinic of the Pediatric Department. Confirmation of lead intoxication was determined through blood lead levels, roentgenograms of the long bones, urinary coproporphyrins, and hemograms. All patients were hospitalized during the study period in the University of Maryland Hospital. Twenty-four-hour specimens of urine were collected for lead determination. Three patients were hospitalized for nine days before treatment was instituted, and during this time six twenty-four-hour urinary lead excretion values were determined on each patient. The remaining two patients each had one twenty-four-hour urinary lead determination prior to the institution of therapy. Urinary lead excretion thereafter was determined in all patients throughout the course of study. The Dithizone method with buffer extraction[5] was used to determine urinary lead. A lumbar puncture was performed at the time of admission. Determinations of sugar, chloride, protein, and cell count were done on the spinal fluid. Hemograms, with particular attention to hemoglobin, leukocyte count, and stippling, were done throughout the study. Serum calcium, phosphorus, and total protein content were measured initially and throughout the study.

Ionizable calcium values were determined from the Hastings nomogram. Electroencephalograms were obtained initially and after completion of therapy. Electrocardiograms were recorded initially, throughout, and at the end of the study.

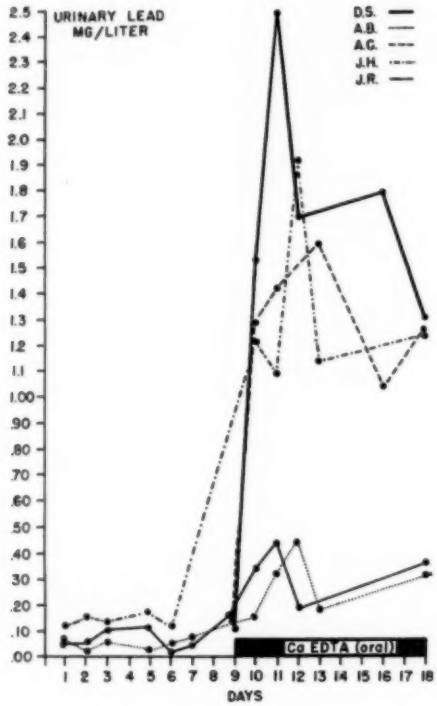

Fig. 1.

The dosage of CaEDTA was 75 mg. per kilogram per day given in divided doses at six-hour intervals. Patients were maintained on the drug for a period of nine days.

OBSERVATIONS

Three patients observed for nine days prior to instituting therapy showed a uniform rate of urinary lead excretion (Fig. 1). The amount of lead excreted ranged from a low of 0.03 mg. (J. R.) to a high of 0.20 mg. (J. H.). Oral CaEDTA produced a significant increase in urinary lead excretion in all patients. The urinary lead excretion on the day following the beginning of treatment was increased three- to tenfold, and maximum excretion was reached between the second and fourth day. After this time, urinary lead was excreted in lesser amounts, but the value obtained at the completion of treatment was still well above any obtained during the pretreatment period. Two patients (A. B. and J. R.) showed a lower rate of excretion than the other three patients. It was our impression

that these two patients showed less effect from lead intoxication than the other three.

TABLE I

PATIENT	BEFORE TREATMENT BLOOD LEAD (MG./100 GM.)	AFTER TREATMENT BLOOD LEAD (MG./100 GM.)
D. S.	0.07	0.06
A. C.	0.083	0.06
A. B.	0.062	0.06
J. R.	0.086	0.064
J. H.	0.125	0.072

The pre- and posttreatment blood lead values are shown in Table I. It is to be noted that three patients had normal values following treatment, and significant reduction occurred in the other two. While the change in environment may have influenced these values to some extent, it does not seem likely that this could be the entire explanation. Rather the increased urinary lead excretion and the lowering of blood lead levels suggest that CaEDTA is absorbed from the gastrointestinal tract. If this is true, the lowered blood lead level would seem to exclude the likelihood of the formation of a lead EDTA complex in the gastrointestinal tract with subsequent absorption.

Urinary coproporphyrins were positive in all patients before the institution of treatment. A. C. who had a strongly positive urinary coproporphyrin before the beginning of treatment showed a negative coproporphyrin on the sixth day of therapy. D. S. had a slightly positive urinary coproporphyrin before treatment; this, however, became and remained negative after the second day of treatment. The remaining three patients had consistently negative urinary coproporphyrins throughout their hospital stay.

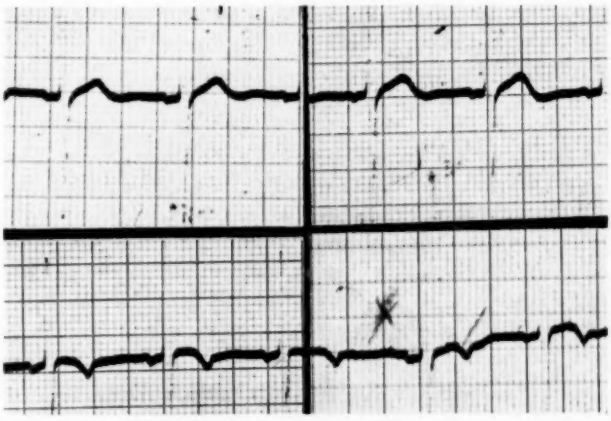

FIG. 2.—Electrocardiograms taken before treatment and on third day after treatment, showing the inversion of T wave in V_1 and V_2 leads.

Four patients showed a microcytic hypochromic anemia which remained unchanged during the period of observation. No alterations were noted in the serum calcium or phosphorus. Ionizable calcium as determined in four patients was normal. Spinal fluid findings were normal in all patients.

Two patients, J. R. and A. C., had abnormal electroencephalograms characterized by high voltage spikes and high voltage slow waves. Three months later the electroencephalograms of these patients were unchanged. J. H. initially had occasional high voltage waves in the frontal area, which were interpreted as borderline. An electroencephalogram done one month after treatment was normal.

Changes in the T wave in the electrocardiograms occurred in four of five patients; namely, J. H., A. C., D. S., and J. R. The change consisted of inversion of the T wave, V_1 and V_2 leads (Fig. 2). In J. R. the T wave was low and notched in both V_1 and V_2. In all cases the electrocardiogram returned to normal after the drug was discontinued. The return to normal occurred anywhere from the second to the fourth day upon cessation of therapy.

Leitch and Haley[6] have studied the effect of chelating agents on the isolated mammalian heart. They concluded that free EDTA has a direct effect on the myocardium but no significant vagal or cholinergic effect.

It is to be remembered that in children, inversion of the T wave in the precordial leads is not an uncommon finding. Children may also switch T direction without known cause. While the significance of the changes observed in the T waves is unknown, it seems reasonable to conclude that they were brought about through the administration of the oral CaEDTA. This conclusion seems justified when one considers that the T-wave changes appeared after the administration of CaEDTA, and then upon discontinuance of the drug the electrocardiogram reverted to its pretreatment pattern.

The CaEDTA was tolerated, and gastrointestinal symptoms, such as vomiting or diarrhea, did not occur in any patients. Improvement in appetite and lessening of irritability after beginning the drug were noted in three patients. Vomiting and blurring of vision, which were present in one patient (A. C.) on the day of admission, disappeared on the second day of treatment. All of the patients treated in this series are free of symptoms of lead intoxication at the present time.

SUMMARY AND CONCLUSIONS

The use of oral CaEDTA given to five patients with proved lead intoxication produced a marked increase in urinary lead excretion. The drug was well-tolerated and brought about disappearance of symptoms of anorexia and irritability. Initial elevated blood lead values were lowered following treatment in all five patients. Changes in the T waves, which were noted in four of the five patients during treatment, disappeared upon discontinuance of the drug. The significance of these changes is not known at the present time.

The amount of urinary lead excreted following oral CaEDTA is much less than that which follows intravenous CaEDTA.[2] This suggests that in acute lead intoxication and in lead encephalopathy where it is necessary to obtain a rapid excretion of lead that the intravenous route should be employed. However, oral CaEDTA may eventually prove of supplementary value and at the present time offers some promise as an

agent in the treatment of chronic lead poisoning. Final dosage, frequency and duration of treatment remain to be determined.

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IRON ABSORPTION IN PREMATURE AND FULL-TERM INFANTS

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THE hemoglobin of both full-term and premature infants falls rapidly from the high values observed at birth to a nadir at 12 to 14 weeks, with the production of a "physiological" anemia (Fig. 1).[3, 4, 13-15] The cause for this decrease is not known, but since deficient absorption of iron from the gastrointestinal tract or faulty utilization following normal absorption can produce anemia, the question arises as to whether poor absorption or subsequent poor utilization is important in these infants. The present investigation deals only with iron absorption and utilization in the neonatal period.

The introduction of radioactive or "tagged" iron by Hahn and associates[6] in 1938 made it possible to introduce a given quantity of iron into the body and follow it through the processes of absorption, utilization, and excretion. Because of this unique property, radioactive iron, F^{59}, with a half-life of forty-seven days, was chosen for the present investigation.

METHODS OF STUDY

In this experiment, fourteen full-term infants weighing more than 2,500 grams and ten premature infants weighing less than 2,500 grams were studied. Included in the premature group were infants of both single and multiple birth, while among the full-term infants only those of single birth were included. The mothers had no known chronic disease, and their pregnancies were normal.

A single test dose of ferrous chloride solution, 6 ml. in volume and containing 200,000 countable counts per minute of F^{59}, was given each infant. The iron in the test dose was present as ferrous chloride and represented approximately 1.0 μg of elemental iron. The solution was maintained in the ferrous state by an excess of ascorbic acid since it has been shown that ferrous iron is the form most readily absorbed from the gastrointestinal tract.[10-12]

All test doses were given by gavage. Full-term infants were given the test dose on the second to the fourth day of life, while all the premature infants received their test dose within the first seven days of life. Any infant who vomited within an hour of administration was dropped from the series.

Two to six weeks after the administration of the "tagged" iron, 5 to 10 ml. of blood was withdrawn from the internal jugular or femoral vein. The blood was then prepared by the method of Hahn[8] and counted with a bell-type Geiger-Müller tube with a thin mica window in conjunction with a M.I.T. counting rate meter.

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Utilization was then calculated as follows:

80 × wt. in kg. = blood volume (B.V.) in ml. (approximate)
(B.V.) × venous hematocrit = circulating red cell mass
Red cell mass × 0.75 = corrected cell mass
Red cell mass × CPS per milliliter of cells

$$\frac{\text{200,000 CPS}}{\text{} \times 100 = \text{per cent of uptake.}}$$

culation of blood volume is only a compromise, but does represent the best one available, and probably contributes no greater order of variation than the other determinations in this study.

RESULTS

In Fig. 2 the birth weight of the infants in pounds is plotted on the

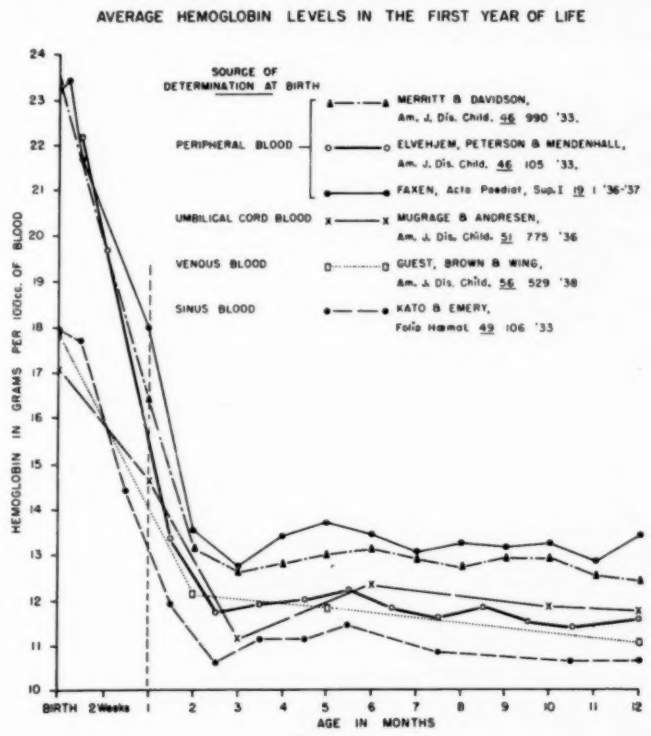

Fig. 1.

Blood volume for these infants was arbitrarily selected as 80 c.c. per kilogram of body weight after the formula of Balfour and co-authors.[2] The red cell volume as calculated from plasma volume and venous hematocrit is too high by about 25 per cent,[9, 12, 17] and, therefore, makes necessary the use of the factor 0.75 to obtain corrected cell mass. It is recognized that this cal-

abscissa and the per cent of the test dose of Fe^{59} absorbed is plotted on the ordinate. A second ordinate is inserted at 5 pounds 8 ounces (2,500 grams) to separate premature and full-term infants. The blood from premature infants contained from 0.29 to 6.8 per cent of the test dose with a mean of 2.8 per cent, while the blood from full-term infants contained from 0.4

to 8.2 per cent of the test dose, with a mean of 3.2 per cent. The difference in iron absorption between the two groups is small in relation to the observed variability within each group and, therefore, appears to be of no significance.

In Fig. 3 the relationship of maternal hemoglobin concentration to the iron absorbed by the infant is plotted to ascertain if there is a correlation between the two.

DISCUSSION

Absorption of iron was noted in all the infants studied. This would seem to indicate that at the time of birth or within one or two days following, the physiological mechanism for the absorption and utilization of iron from the gastrointestinal tract is present and functioning.

Darby and co-workers[1] studied the percentage uptakes of a single test dose

PER CENT OF TEST DOSE OF IRON 59 ABSORBED BY PREMATURE AND FULL TERM NEWBORN INFANTS IN RELATION TO BIRTH WEIGHT

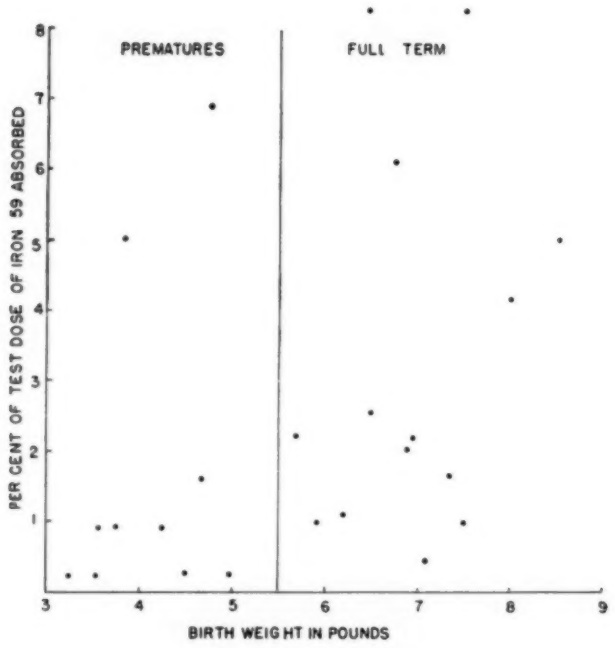

Fig. 2.

The observed data do not suggest that there is a relationship between maternal hemoglobin values and per cent of the test dose of iron contained in the infant's blood. The factor of multiple births also seems irrelevant (Fig. 2).

of "tagged" iron fed to school children of 7 to 10 years of age, inclusive, and found that it varied, averaging from 7.75 to 17.75 per cent of a test dose of 2 to 3 mg. of ferrous iron. Moore and associates[16] reported that absorption in normal adult males

ranged from 1.1 to 11.2 per cent. In contrast, Hahn and co-workers[7] found that pregnant women absorbed from 18 to 36 per cent of a single test dose, and Moore[16] reported that males with iron deficiency anemias absorbed 11.9 to 39.7 per cent of a single administered dose.

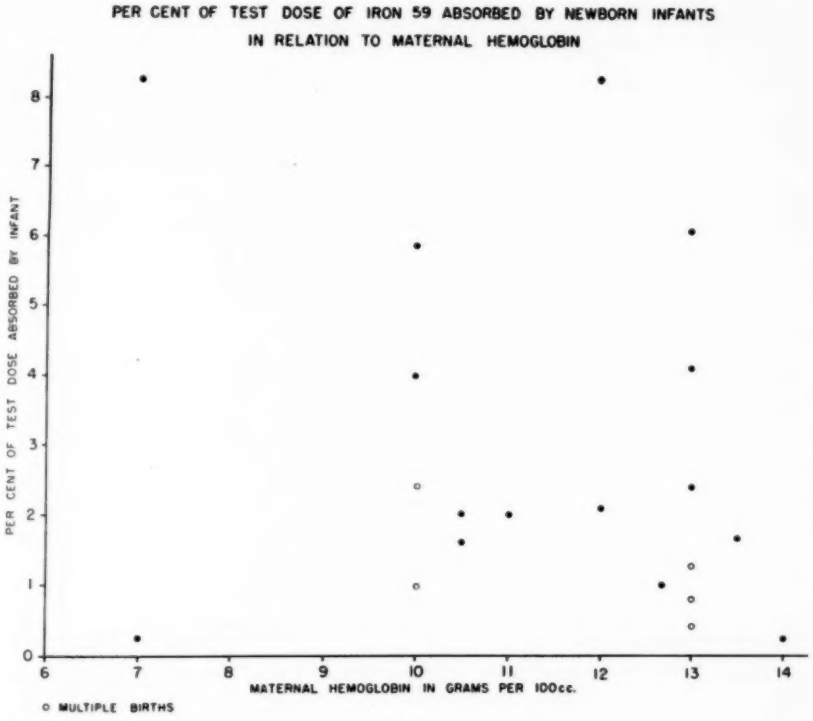

Fig. 3.

It, therefore, can be estimated that from the above-quoted papers normal patients absorb for the most part less than 10 per cent of a single test dose of "tagged" iron, while patients with an abnormal demand show absorption of greater amounts.

If we accept the values of less than 10 per cent as representing normal needs and those greater than 10 per cent as representing abnormal needs, it would seem that newborn infants do not have greater needs for iron than do normal adults. Another possibility which should be taken into account, however, is that although the mechanism for absorption and utilization is present and functioning at the time of birth, it is not sufficiently developed to function at a higher level than that observed. The first explanation, relating the low values observed to low needs, seems the most probable.

CONCLUSIONS

1. The mechanisms for the absorption of iron from the gastrointestinal tract and its incorporation into hemo-

globin are present and functioning at the time of birth.

2. There is no relation between the mother's hemoglobin at the time of birth and the amount of iron absorbed by the infant.

3. All infants studied showed absorption and utilization of infinitely small quantities of elemental iron. The values obtained cannot be translated to cover larger amounts.

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FOLLOW-UP OF INFANTS BORN OF TREATED SYPHILITIC MOTHERS

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SINCE the introduction of penicillin as an antispirochetal agent, the incidence of congenital syphilis in infants born of treated syphilitic mothers has diminished considerably. This study was undertaken in order to determine how the effectiveness of therapy as administered to mothers at our hospital compared with that elsewhere. One hundred cases of infants born of treated syphilitic mothers were picked at random from the files of the out-patient department of Lincoln Hospital. In all of these cases the mothers were treated with penicillin. Fifteen additional cases were included in which the mothers received combined bismuth and Mapharsen therapy. For convenience the cases have been grouped according to the month of gestation in which the mother received therapy, i.e., before the seventh month, during the seventh month, during the eighth month, and during the ninth month. The dosage and mode of administration of penicillin varied somewhat because the patients were neither treated during the same year nor were they all treated during a period when one particular plan of therapy was popular. The follow-up on these cases varied from two months to three years eleven months. Ninety-two of the 115 infants were followed for four months or more. All those followed in the penicillin-treated group of 100 cases had negative serologies at birth except three. Two showed a reversal of their serologies untreated and did not have syphilis.

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DISCUSSION

This series includes thirty-five cases in which the mother was given antisyphilitic therapy prior to the seventh month, nineteen cases treated during the seventh month, thirty-four cases during the eighth month, and twenty-seven cases during the ninth month. The only syphilitic infant born was one of a woman treated in the ninth month. The Kline, Mazzini, and Wassermann tests were used by this institution. Six of the infants born to these treated syphilitic mothers were seropositive at birth. The remaining 109 cases were seronegative during the time that they were followed.

In the 100 cases where the mother received penicillin therapy, three infants (3 per cent) were born with a positive serological test for syphilis. Two of these mothers were treated before the seventh month and one mother was treated during the ninth month. The infants of the two mothers treated before the seventh month showed a spontaneous reversal of serology. This could indicate that the initial positive serological test for syphilis was due to the transfer of reagins from the mother rather than an actual infection. One of these infants received penicillin antisyphilitic therapy because of suspicious

mucocutaneous lesions. In this case, the mother had been treated during the ninth month of gestation. Possibly the placenta here was diseased and there was poor transmission of penicillin in utero at this time. This is our only penicillin failure.

Of the fifteen cases in which the mothers received combined Mapharsen and bismuth therapy, three of the infants (20 per cent) were born with

The percentage of nonsyphilitic infants (99 per cent) born to syphilitic mothers treated with penicillin in this series compares favorably with the figures given by Goodwin and Farber[1] (100 per cent) of live children, by Wammock and associates[2] (94.5 per cent), by Shaffer and Courville[5] (98.9 per cent), by Speiser[6] (98.2 per cent), and by Turner[7] (100 per cent). However, it must be pointed out that

TABLE I

	NUMBER OF CASES	THERAPY GIVEN TO MOTHER	NUMBER OF INFANTS WITH POSITIVE SEROLOGY AT BIRTH	NUMBER OF INFANTS WITH POSITIVE SEROLOGIES THAT REVERSED	INFANTS WITH X-RAY EVIDENCE OF BONE LESIONS	NUMBER OF SERO-POSITIVE INFANTS RECEIVING PENICILLIN THERAPY
Infants born of syphilitic mothers treated prior to the seventh month of gestation	35	Penicillin 26 cases	2	2	None	
		Bismuth and Mapharsen 9 cases	2	1	Calcified periostitis	1
Infants born of syphilitic mothers treated during seventh month of gestation	19	Penicillin 15 cases	0		None	
		Bismuth and Mapharsen 4 cases	1	No follow-up	Periostitis	0
Infants born of syphilitic mothers treated during the eight month of gestation	34	Penicillin 31 cases	0	0	None	0
		Bismuth and Mapharsen 3 cases	0	0	None	0
Infants born of syphilitic mothers treated during the ninth month of gestation	27	Penicillin 17 cases	1	0	None	1
		Bismuth and Mapharsen 10 cases	0	0	None	0

a positive serological test for syphilis. One infant whose mother was treated prior to the seventh month apparently had a spontaneous reversal in serology. The second infant whose mother was also treated prior to the seventh month was treated with penicillin after which she was seronegative. In the third case, no follow-up was possible.

some of these authors[2] classified cases according to whether the mother had early or late syphilis. According to Wammock and associates[2] the percentage of seronegative infants was greater in the group of mothers with late syphilis.

Positive x-ray findings were reported in three cases. In one of these, the mother had been treated with

bismuth and Mapharsen and the infant was seropositive at birth. In the other two cases with x-ray findings, the serological test for syphilis was negative. These children did not have active syphilis at birth.[5]

The question of adequate dosage of the antispirochetal agent often arises. It is generally agreed that 2.4 million units or more of penicillin is adequate for the syphilitic pregnant mother.[1] Adequate metallotherapy had been considered to be of a total of 0.5 to 0.6 Gm. of Mapharsen and 1.2 Gm. of bismuth.[3, 4]

All of the syphilitic mothers in our group who were treated with penicillin received 2.4 million or more units, with the exception of two cases in which there were reactions to penicillin. Of our 100 cases, ninety-six patients were treated for six to fifteen days, two for five days, one for three days, and one for two days.

Therapy in these last two cases was terminated after each mother had received a total of 900,000 and 600,000 units of penicillin, respectively. One of the infants' serological test for syphilis was recorded as plus minus at 9 months of age and the other negative at 7 months of age. These children did not have syphilis.

SUMMARY

One hundred syphilitic mothers were treated with penicillin at various times during their gestations and their offspring followed for varying lengths of time. Fifteen infants of syphilitic mothers treated with bismuth and Mapharsen were also followed. Three per cent of the group whose mothers were treated with penicillin were seropositive at birth, but only one of these infants had syphilis and required penicillin therapy for congenital syphilis while the other two had a spontaneous reversal of the serological test for syphilis. These figures compare with those reported by other workers. Of the infants whose mothers received bismuth and Mapharsen 20 per cent were seropositive at birth. One of these showed a spontaneous reversal of serology, a a second received penicillin therapy for congenital syphilis, and a third could not be followed.

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HOW SAFE IS X-RAY AND FLUOROSCOPY FOR THE PATIENT AND THE DOCTOR?

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X-RAY and fluoroscopy are well-established procedures in the examination of patients by most physicians and especially many pediatricians. The trained radiologist is today well acquainted with the dangers and limitations of fluoroscopy, but this is usually not true of the occasional user of x-ray and fluoroscopic equipment. With the birth of the atomic age and its rapid growth and development there is a greatly increasing number of persons now being exposed to ionizing (destroying) radiation of all kinds. This makes it imperative that every effort be made to provide adequate protective and measuring devices for physicians and patients and others exposed to radiation and that they be properly instructed as to their use.

The effects of x-radiation on biological tissues are generally deleterious; therefore, radiation to which a patient is exposed should be maintained at low values. The injurious effects may be either local or systemic. Skin lesions are well known. Carmen and Muller[1] in 1924 warned of the attendant hazards, especially to the blood and blood-forming organs, anemia and sterility from overexposure to x-ray during fluoroscopy. March[2] stated that the evidence of leukemia in radiologists over a fifteen-year period was about ten times as great as the evidence of this condition in nonradiologists. The ratio is also high in dermatologists. There is a small but persistent incidence of radiation damage in dentists who hold films in the mouth of a patient. Recent reports claim the incidence of leukemia in physicians as a group is three times that of a comparable age group of laymen. Of 135 physician patients seen at Mayo Clinic[3] for local x-ray injuries only eight had received previous x-ray training and none had followed the recommended protective measures. Most of these injuries were received at a single prolonged examination such as reducing a fracture or finding a foreign body.

In 1942 Buschke[5] broached the question of the potential danger of routine fluoroscopy in infants on the theory that they were receiving too much radiation. At that time he had no accurate means available for these measurements. A recent paper by Miller[16] stresses this potential danger by the inexperienced operator. This study will attempt to answer some of these hypotheses. Precise measurements now available reveal that infants routinely fluoroscoped by a good x-ray machine receive one-tenth as much radiation per examination as Dr. Buschke and Dr. Miller had presumed (0.3 r. instead of 3.0 r. per individual examination).

Read before the King County Medical Society, Seattle, Oct. 6, 1952.
Read before the 7th International Pediatric Conference, Havana, Cuba, October, 1953.
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The amount of scatter radiation received by the operator during fluoroscopy (weekly, over a one-year period) was measured by Tracerlab badges worn over the chest, pubic region, and feet. The results show that more than 0.4 r. was received over the chest, while 0.45 r. was received at the pubic region per week. With additional simple lead shielding on the sides of the machine the amount of radiation was cut to 0.1 r. per week, about one-fourth the previous exposure. Practically no radiation penetrates the viewing screen.

Table I. Comparative Radiation Dosages

X-ray picture chest—office	0.1 r.*
X-ray picture chest—truck	5 to 10 r.
X-ray fluoroscopy—chest	0.25 to 0.5 r.
X-ray and fluoroscopic—gastrointestinal examination	20 to 40 r.
X-ray teeth (mouth—jaws)	10 r.
X-ray treatment boil or acne (localized)	50 to 1,000 r.
X-ray treatment skin cancer (localized)	5,000 r.
X-ray treatment internal cancer (localized)	100,000 to 1,000,000 r.

This amount of radiation is received by local treatment *or a radiography of a single area either in one or multiple treatments. Therefore, these doses are reasonably safe if not repeated too often.*

*r. = roentgen—unit of measurement of radiation.

Table II. Total Radiation of Whole Body (Such as an Atom Bomb Explosion) or Prolonged X-ray (Gamma Ray) Exposure

Human being	Fatal dose	300 to 600 r.
Mouse	Fatal to 50%	500 r.
Guinea pig		250 r.
Rabbit		825 r.
Fish		1,200 r.

A small dose of *total* radiation is much more dangerous than the same dosage in a local small area. The tolerance of animals varies. Fish and rabbits require two to three times the total radiation of human beings for fatal effect.

Composite measurements of the radiation received over various areas of the body for many weeks, as measured by the radiation badges, revealed these facts: The pubic area and the left chest received more radiation than the right chest and the back because they are closer to the tube. This is to be explained because these areas are more exposed to scatter radiation from the rays between the table top and the screen and the table top and the tube underneath. (The operator stands in front and near the foot of the table and manipulates the screen with his right hand while the left hand regulates the shutter mechanism.)

With these facts before us, it becomes of great importance that the physicians using radiation for x-ray films or fluoroscopy should know the hazards and risks involved for his patient, as well as himself. He should know the capabilities of his x-ray equipment and the amount of radiation he is receiving. He should also know what represents a "tolerance dose." During the war a film badge[6] (Tracerlab) was developed for health monitoring of workers in radioactive fields. This packet contains two films for measurement of radiation dosage from 0 to 30 r. (modified for gamma [X] rays).

The badge is worn by the patient or operator for a known period of time.

Weekly measurements are made of the x-ray dosage by comparing the developed film with a known roentgen graph and the resulting roentgen dose read directly. The badge was worn (by the various physicians) over selected parts of the body to detect scatter rays above and below the x-ray machine. This study required hundreds of badges over a two-year period, and all tests were repeated several times. Patients of various ages who came in for routine examinations were used as subjects.

Badges were used by various medical specialists, nurses, x-ray technicians, veterinarians, and dentists as well as on shoe machines. Most operators were within normal safety limits, receiving less than 0.3 r. per week of stray radiation. One of the leading roentgenologists averaged two to three times the weekly maximum safety dosage.

The physical problems of fluoroscopy may be divided into two principal categories: (1) those concerned with radiation hazards to which the patient and the physician are exposed during the examinations, and (2) those concerned with poor visibility during the fluoroscopic examination. The following factors are of utmost importance. The diagnostic study should be carried out where the (1) field of vision is restricted by the fluoroscopic shutters to the smallest size consistent with adequate vision. (2) The time of exposure should be reduced to the shortest possible interval consistent with a complete examination. (3) Other factors

TABLE III. NATIONAL SAFETY STANDARDS FOR RADIATION: REPORT OF NATIONAL RADIATION COUNCIL (1949)

Maximum daily exposure	0.05 r.
Maximum weekly exposure	0.3 r.
Maximum annual exposure	15.0 r.

TABLE IV. RADIATION RECEIVED BY THE OPERATOR DURING ROUTINE FLUOROSCOPY OF CHILDREN*

	NO. OF FLUOROSCOPY EXAMINATIONS	TIME TOTAL (MIN.)	EXPOSURE (HOURS)	NO. OF "r"
Day	25	6 to 12	0.1 to 0.2	0.05
Week	125	60	1.0	0.250
Year	6,000	2,880	48.0	12.0

Number of examinations per day, 25; 5-day week; time, 30 seconds.
75 KVP—2 mm. Al filter—4 Ma. current
17 in. tube table distance—100 sq. in. screen

*During routine fluoroscopy the operator received 0.05 r. per day, 0.250 r. per week, and 12 r. per year. This is less than the maximum allowable safety standards suggested by the National Radiation Council. With experience, the amount of radiation received was cut two-thirds by reducing the time of fluoroscopy to an average of about ten seconds without any loss of efficiency.[3] These figures are based on actual measurement of radiation over a two-year period. Protection against radiation has been very successful.

TABLE V. THE AVERAGE ANNUAL EXPOSURE* IN THE TEN HIGHEST AND WORST CASES AT THE HANFORD ATOMIC PLANT

1945	1.5 r. per year
1948	2.0 r. per year

*In 1945 the average *annual* exposure for *all* employees was 0.9 r. for the entire year. This was reduced by proper and adequate health monitoring to 0.3 in 1948. Any employee receiving more than 0.1 r. per week had his job changed to a safer area. These figures show that with proper protection the amount of scatter and stray radiation can be cut to a very low minimum. These employees, even those most exposed, received less radiation in one year than the average physician (who does routine fluoroscopy) receives in one week.

must be known such as the kilovolts applied to the roentgen tube, (4) the target-table top distance, and (5) the filtration to the roentgen beam. These factors influence the quantity of irradiation to which the patient is subjected.

In general, procedures that reduce the radiation exposure to the patient also reduce exposure to the fluoroscopist. Additional aids are lead rubber gloves and aprons, but these do not protect the head, neck, and shoulders. No manufacturer of fluoroscopic equipment publishes such data to reduce exposure at the present time.[7] The lead glass covering the screen appears to be effective in preventing the transmission of significant quantities of direct radiation to which the doctor is exposed.

Biophysicists[8] who have recently expressed so much concern over the delivery of even minute quantities of x-radiation to the body may be unnecessarily apprehensive. Kaplan[14] treated 400 women with therapeutic x-ray for female sterility. One hundred eighty-three perfectly normal children were born in this first genera-

TABLE VI. AMOUNT OF RADIATION ABSORBED IN ROUTINE FLUOROSCOPIC EXAMINATION OF CHILDREN. APPROXIMATE AVERAGE NUMBER OF "R." (ROENTGEN) UNITS

AGE CLASSIFICATION	FOR SINGLE EXAMINATION	TOTAL ANNUAL EXAMINATIONS	
		NUMBER OF EXAMINATIONS	r. UNITS
Infant (to age 1 year)	**0.250 r.**	**8 to 9**	**2.5**
Toddler	**0.250 r.**	**2 to 3**	**0.5 to 1.5**
Preschool	**0.300 r.**	**1 to 2**	**0.3 to 0.7**
School	**0.310 r.**	**1**	**0.3 to 0.5**
Total (from birth to 6 years)		12 to 14	3.6 to 5.7

250 to 300 milliroentgens (0.25 to 0.30 r.) per single examination was the average amount of radiation exposure.

Over a six-year period, from infancy to school age, a child received an average total of about 3.6 to 5.7 r. radiation. This is well within safe limits and compares quite favorably with the operator who received from 60 to 70 r. over this same six-year period.

TABLE VII. X-RAY OUTPUT OF SEVEN MACHINES USED FOR FLUOROSCOPIES IN INFANTS (BUSCHKE)*

EQUIPMENT	NOMINAL CURRENT (Ma.)	AVERAGE DOSE RATE ON SKIN (r. PER MIN.)	AVERAGE DOSE RATE 5.5 CM. DEEP (r. PER MIN.)	NOTES
A	5	6.0	1.2	
B	No milliameter	6.3	1.9	Output variable
C	5	16.0	Not measured	Output so variable that screen brilliancy changed
D	3	28.0	4.0	
E	5	35.0	Not measured	Tube current varied freely from zero to 40 Ma.; output dangerously erratic
F	5	37.5	3.8	
G				
Operator 1	3	23.0	4.0	Two technicians used different
Operator 2	5	38.0	7.0	technique on same machine

*This table, taken from Dr. Buschke's[3] article, shows the amount of radiation given off by various pediatricians' machines in 1942. A few of these x-ray machines were retested recently and show that the amount of radiation is still excessive, in some cases about five times the safe dosage (as used during routine fluoroscopy).

tion. Three normal children have been born to the second generation. Conclusions drawn from experiments on flies may not be applicable to human beings. Too many and too prolonged fluoroscopic examinations such as in repeated gastrointestinal studies may be harmful (5 to 15 minutes, 20 to 40 r., per each series).

Some destructive changes are produced by very small doses.[11] These are irreversible and cumulative. Skin changes may occur as long as twenty-five years after exposure ceases. As little as 0.8 r. daily may cause skin changes (some changes in blood may result from weekly exposures of 0.1 r.).

Templeton,[9] in his excellent book *X-ray Examination of the Stomach,* states that screens of 30 to 50 square inches present no clinical problem in the examination of any anatomical structure (screen size 7 by 7 or 5 by 6 inches). Morgan[7] declares that "Investigations indicated that almost all the intelligence recorded on a fluoroscopic screen is appreciated by the observer within a few seconds after the image has appeared on the screen. Long periods of further scrutiny are usually of little value in determining additional diagnostic information. The speed of intelligence appreciation by an observer depends on his experience."

A national standardized radiation diary system has been recommended.[15] This diary would contain a record of all previous radiation exposures for any individual patient. It would include exposures to x-ray, diagnostic (including dental), therapeutic, industrial. occupation, military, also radium and isotopes, as well as all other forms of radiation. The patient would retain this record. The danger to the chance observer or the patient is negligible. It is the daily exposure month after month and year after year from which the physician must be guarded. Fortunately, protection against scattered radiation is easy to attain by present technique.

RECOMMENDATIONS TO REDUCE RADIATION EXPOSURE

1. A good x-ray machine, properly adjusted by experts for kilovolt peak, filters, meter angle, tube target distance, time exposure, and protection against scatter radiation.

2. Smaller screen opening, approximately 50 square inches instead of 200.

3. Protection under table, between tube and table top and screen.

4. Longer intervals for eye accommodation.

5. Shorter examination periods and fewer (?) examinations.

6. Lead and rubber protecting gloves, aprons, etc.

CONCLUSION

All physicians should learn the dangers of radiation as well as its usefulness. They should understand the means of preventing injury and observe the simple rules for protection. This is necessary for their own as well as for their patients' continued good health.

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CONGENITAL ANOMALIES OF THE ANUS AND RECTUM

The Recognition and Management

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PERHAPS the infrequency of congenital anomalies of the anus and rectum justifies a certain amount of indifference on the part of the busy physician, particularly when more common disease processes occupy his attention. However, one out of 5,000 babies born will have a malformation of the anus or rectum and some authors claim the incidence to be as high as one in 1,500 births.[1, 2, 3] This means that in the United States more than 750 babies are born each year with one of these defects.

Infants with anomalies of the anus and rectum present serious problems which, nevertheless, can be solved if the physician is familiar with the conditions. Therefore, I propose to discuss the recognition and management of malformations of the anus and rectum with particular attention to recent advances in treatment.

EMBRYOLOGY

In order to better understand how perversions of development lead to anomalies of the anus and rectum, let us briefly review the normal embryology of this region (Fig. 1).[4, 5, 6, 7, 8] In the 5-week-old embryo the future urogenital and intestinal tracts join in a common terminal cavity, the cloaca, which is closed to the exterior by the cloacal membrane. Thus, the anterior bladder and urogenital sinus are connected to the posterior hind-gut. During the sixth week a bridge of mesoderm, known as the urorectal septum, grows down between the urogenital sinus and rectum, reducing the connection between the two systems to a small passage, the cloacal duct, and by the seventh week separation is complete. Late in the seventh week, the urogenital sinus acquires an opening to the exterior, but the rectum is still closed off by the anal membrane. During the eighth week an invagination of the ectoderm at the site of the future anus, known as the proctodeum, occurs and during the eighth week or early in the ninth week the ectodermal proctodeum joins the entodermal rectum, the anal membrane ruptures, and the intestinal tract obtains a caudal opening to the outside world. The site of union of the proctodeum and rectum is marked by the white line of Hilton.

Knowing the pattern of normal development, we can understand how some of the anomalies result from arrested or abnormal development during the seventh or eighth week of embryonic life.[1] Should the anal membrane fail to rupture completely, anal stenosis might result. If the membrane persists in entirety, membranous imperforate anus will occur. Should the rectum fail to descend, or should the posteroinferior portion

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of the cloaca be involved in a degenerative process, we may conjecture that a rectum which ends blindly at a considerable distance above the perineum might result. Further, we can readily understand how fistulas between the rectum and genitourinary system would occur if the urorectal septum failed to sever completely the communication which is present normally in the embryo of six weeks. In the female, the Müllerian ducts, from which the uterus and vagina are derived, grow into the urogenital sinus along the dorsal wall and thus may acquire already existing fistulas between the rectum and urogenital sinus.

It should be emphasized that the external anal sphincter muscle develops from the regional mesenchyme, independent of the development of the rectum and anus. Thus, the sphincter is probably present in all types of imperforate anus and the presence of the muscle can be depended on in considering treatment with the establishment of a normally functioning anus as the goal.[1, 8, 9, 10]

Finally, no relationship between the occurrence of maternal illness during pregnancy and the occurence of imperforate anus has been demonstrated. The abnormalities usually do not run in families, indicating an absence of hereditary influence.[3]

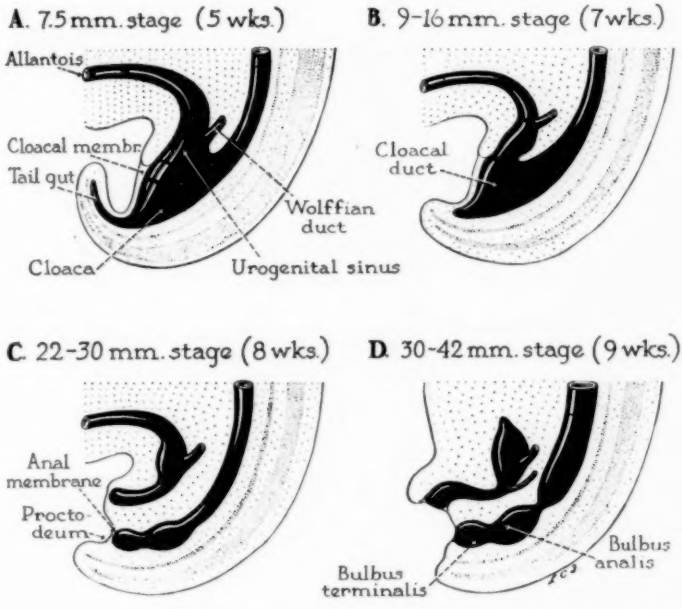

Fig. 1.—Stages in the normal development of the anus and rectum. (After Ladd and Gross, from Eckerle: Am. J. Surg., Nov., 1951.)

TYPES

With the exception of certain extremely rare conditions such as median band of the anus, congenital anomalies of the anus and rectum fall

into one or another of four groups (Fig. 2).[6] Type 1 is characterized by a patent anus and rectum with stenosis of the anus or lower rectum. In the type 2 group, the anus is imperforate, but only a thin membrane occludes the opening. The characteristics of type 3 are an imperforate anus with a rectal pouch blindly ending some distance above the perineum. The fourth type is distinguished by a normal anus and lower rectum, with the remainder of the rectum ending blindly and separated from the lower pouch by a variable distance.

Since the 1920's only three reports in which more than 100 cases of imperforate anus have been studied have appeared in the literature. Table I shows the incidence of each of the four types in the studies of Mayo and Rice,[11] of Moore and Lawrence,[3] and of Gross.[1] The distribution of cases in each series is very similar. If we combine the results of each report, we find that the type 3 malformation, that is, the one in which the rectum ends blindly above an imperforate anus, is the most common, with an incidence of 79 per cent of the total. This is significant because the treatment of this type is fairly difficult. Fortunately, the fourth type, which is the most difficult to treat, is the least common. On the other hand, type 1 is also not frequent, and it requires the simplest treatment. The incidence of these malformations in males and females is about equal.[1, 11, 12]

TABLE I. INCIDENCE OF THE TYPES OF ANORECTAL ANOMALIES

AUTHOR	NUMBER OF CASES				TOTAL
	TYPE 1	TYPE 2	TYPE 3	TYPE 4	
Mayo-Rice (1950)	4	62	95	4	165
Moore-Lawrence (1952)	5	20	90	5	120
Gross (1953)	29	14	443	21	507
Total (per cent)	5	12	79	4	

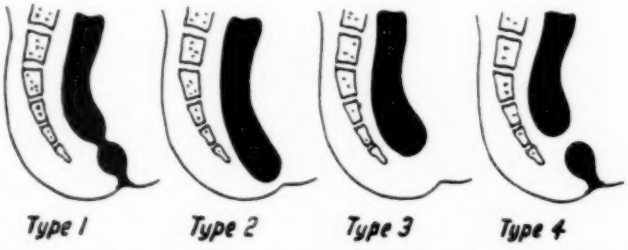

Fig. 2.—Types of malformations of the anus and rectum. *Type 1*, Stenosis of the anus or lower rectum. *Type 2*, Imperforate anus due to a membrane. *Type 3*, Imperforate anus with a rectal pouch blindly ending some distance above the perineum. *Type 4*, Normal anus and lower rectum with the remainder of the rectum ending blindly.

FISTULAS

As indicated in the discussion of the embryology of this region, fistulous connections between the rectum and the genitourinary tract or perineum might well be expected, and they occur in more than one-half of the cases (Table II).[11, 3, 1] These may be rectovesical, rectourethral, rectoperineal, or rectovaginal (Fig. 3). In the vagina the connection may be high or may be with the fossa na-

vicularis at the outlet. It is extremely rare for more than one fistula to be present in a patient.

Frequently the fistula is too small to adequately decompress the bowel and will admit only a small probe. Sometimes the fistula is large enough to permit evacuation of the rectum in the early days of life when the stools are soft or liquid, but later becomes the site of fecal impactions leading to intestinal obstruction and repeated hospitalization. Nevertheless, a number of cases have been reported in which the patients have lived to adulthood without treatment. A significant number of patients have adequate bowel movements through their

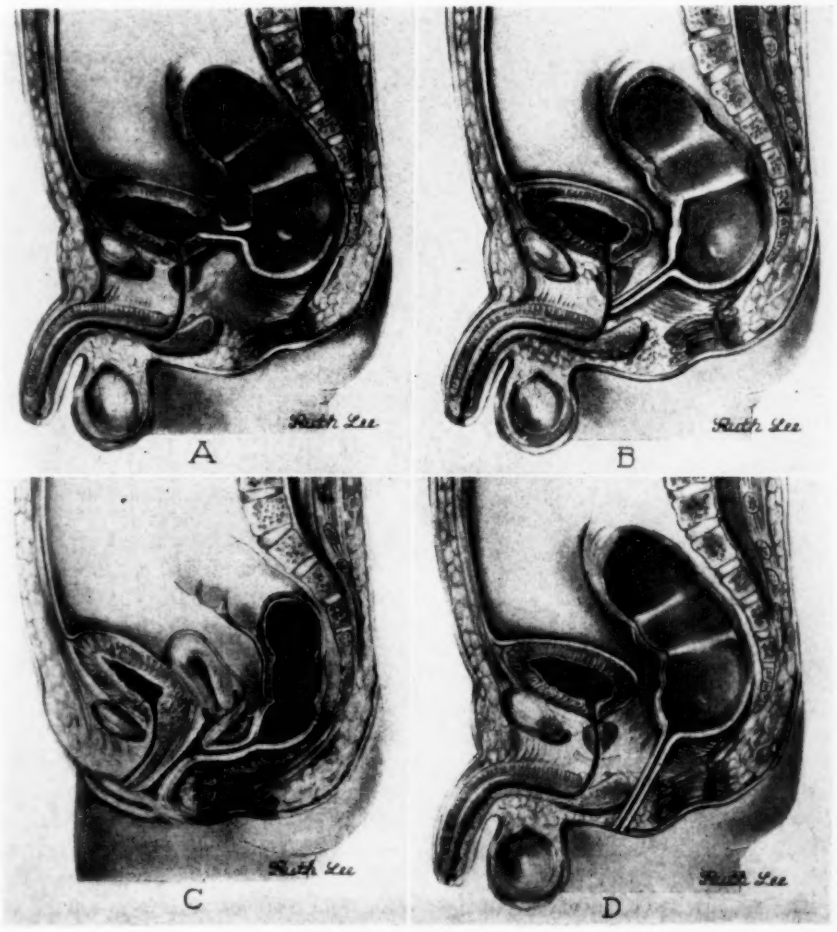

Fig. 3.—Types of fistulas associated with anorectal anomalies. *A*, Rectovesical fistula. *B*, Recto-urethral fistula. *C*, Rectovaginal fistula. *D*, Rectoperineal fistula. (Redrawn from Ladd and Gross: Abdominal Surgery of Infancy and Childhood, W. B. Saunders Co., by Arnheim, Am. J. Surg., May, 1951.)

fistulas, although rectal continence is rare. In untreated patients, particularly in those with connections between the rectum and urinary tract, there is always the danger of urinary tract infection which is unresponsive to drug therapy.

TABLE II. INCIDENCE OF FISTULAS

AUTHOR	TOTAL CASES	PATIENTS WITH FISTULAS	PER CENT FISTULAS
Mayo-Rice (1950)	165	136	82
Moore-Lawrence (1952)	120	70	58
Gross (1953)	507	362	71

rectovesical fistula is less common, and the rectoperineal fistula occurs least often, although it is by no means infrequent. The majority of females with fistulas have connections between the rectum and vagina, less often between the rectum and perineum. Urinary tract fistulas are rare in females. Thus in the male, we should always be suspicious of the existence of recto-urinary tract communications, and in the female we should look first for connections with the vagina. The type 3 patients are the ones who most consistently have fistulas (Table IV). Type 2 patients

TABLE III. DISTRIBUTION OF FISTULAS IN MALES AND FEMALES

AUTHOR	RECTOURETHRAL		RECTOVESICAL		RECTOPERINEAL		RECTOVAGINAL	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Mayo-Rice	39	1	17	4	4	10	0	61
Moore-Lawrence	11	0	13	1	7	9	0	29
Gross	59	0	56	1	54	49	0	143
Total (per cent)	42	0.3	33	1.7	25	22	0	76

TABLE IV. INCIDENCE OF FISTULAS IN EACH OF THE MAJOR TYPES OF MALFORMATIONS

AUTHOR	PER CENT OF CASES WITH FISTULAS			
	TYPE 1 (%)	TYPE 2 (%)	TYPE 3 (%)	TYPE 4 (%)
Mayo-Rice (165 cases)	50	86	81	100
Moore-Lawrence (120 cases)	0	25	71	20
Gross (507 cases)	14	14	80	0
Santulli (62 cases)	0	33	81	0
Norris et al. (52 cases)	0	23	70	0

From the combined statistics shown in Table III we can conclude that the most common fistula in the male is the recto-urethral.[11, 3, 1] Forty-two per cent of the males who had fistulas had this type of communication. The sometimes have fistulas. Despite the report of Mayo and Rice, the consensus is that type 1 and type 4 patients usually do not have fistulas.[1-3, 10-13]

ASSOCIATED CONGENITAL ANOMALIES

Imperforate anus probably more than any other congenital defect is often associated with other congenital anomalies.[14] Table V shows the incidence to vary from 34 to 72 per cent of the cases studied by various authors.[3, 11, 1, 10, 13] Not infrequently, multiple congenital defects have been found in a single patient. Many of these associated anomalies are not serious; however, the mortality rate from associated malformations is fairly high and the over-all prognosis is seriously affected.

Anomalies of the urinary tract, excluding fistulas, are the defects which

occur most frequently in association with imperforate anus (Table VI). For this reason, it is wise to routinely perform urinary tract studies when investigating a patient with an anal or rectal malformation. Abnormalities of the spine and congenital heart disease are not uncommonly found to be associated. Atresias elsewhere in the intestinal tract, particularly esophageal atresia with tracheoesophageal fistula, sometimes occur, necessitating repair of the esophageal lesion before treatment of the rectal abnormality is undertaken.[15] Passage of a rubber catheter into the stomach to test the patency of the esophagus is recommended as a routine measure in the work-up of patients with imperforate anus.

Table V. Incidence of and Mortality Due to Associated Congenital Anomalies

AUTHOR	NO. OF CASES	PER CENT WITH ASSOCIATED ANOMALIES	PER CENT MORTALITY DUE TO ASSOCIATED ANOMALIES
Moore-Lawrence	120	72	19
Mayo-Rice	165	44	3
Gross	507	39	8
Santulli	62	34	6
Norris et al.	52	46	15

Table VI. Incidence of Various Types of Associated Congenital Anomalies

AUTHOR	TYPE OF ASSOCIATED ANOMALY (PER CENT)				
	URINARY TRACT	VERTEBRAL-NEUROLOGICAL	ALIMENTARY TRACT	CARDIOVASCULAR	ALL OTHER
Mayo-Rice (165 cases)	32	17	3	14	34
Moore-Lawrence (120 cases)	28	22	14	10	26
Gross (507 cases)	16	16	18	14	36

SYMPTOMS

Often, anorectal malformations are discovered by the pediatrician or obstetrician in the process of a routine physical examination in the first few days of life. Sometimes attention is called to the abnormalities during an attempt by the nurse or mother to take the infant's temperature. The symptoms are largely a function of the type of anomaly and the presence or absence of fistulas. The type of abnormality often determines the time at which a physician will first be consulted.

Type 1 patients with anal or rectal stenosis often are not first seen until they are several months and sometimes several years old. The physician is consulted because the infant is chronically constipated, passes "ribbonlike" stools, and cries and strains during each act of defecation. The symptoms of intestinal obstruction are not present, although, if the stenosis has existed for a long enough time, abdominal distention due to dilatation of the bowel will be found.

Patients with a type 2 abnormality, an imperforate anus due to a membrane, are seen within the first few days of life because of the usual symptoms of complete intestinal obstruction and because they have never passed meconium. Abdominal distention and vomiting occur by the

second or third day after birth, and if the abnormality is not immediately corrected, they deteriorate rapidly.

Patients with the imperforate anus and blindly ending rectal pouch which characterize type 3 are seen within the first few days of life because of intestinal obstruction like type 2 cases.

Because the anus is normal and the obstruction occurs in the lower rectum out of sight, the abnormality in type 4 cases is often not recognized until the fourth or fifth day of life, by which time the full-blown picture of intestinal obstruction is present, and the patients are dehydrated and toxic. As a result, operation, although emergent, is considerably more hazardous.

Fistulas, when present, may alter completely the picture of imperforate anus, as well as produce additional symptoms. If the fistula is large enough to adequately decompress the bowel, the child may not be seen until later in life at which time pain on defecation, chronic constipation, incontinence, and the fact that feces come from an abnormally located orifice direct attention to the malformation. Fistulas communicating with the urinary tract frequently produce the symptoms of urinary tract infection, particularly of pyelonephritis.

DIAGNOSIS

The diagnosis of anorectal malformation is often obvious from the history. When the mother or nurse relates that she is unable to find an anal orifice and that the infant has not passed a stool, simple examination of the perineum will surely justify the suspicion that such an abnormality is present. A history of feces coming from an opening which is not in the usual location, or from the penis or vagina indicates the presence of a fistula.

The findings on physical examination other than those confined to the anal region depend on whether or not partial or complete intestinal obstruction is present. If obstruction is complete, and if the child is 2 or more days old, the classical signs of intestinal obstruction, including abdominal distention, intestinal patterning, borborygmus, hyperactive peristalsis, tympanites, and later dehydration and collapse, will be found. If obstruction is partial, such as in the type 1 case with anal stenosis or in the type 3 case with a narrow fistula, abdominal distention is found, and not infrequently dilated loops of bowel filled with hard masses of feces may be palpated.

In the type 1 case, a stenotic, even pinhead-sized anal orifice may be seen or the point of narrowing may be felt higher up on rectal examination. In the Type 2 patient, the membranous imperforate anus is obvious and sometimes the dark meconium can be seen through the membrane. When the infant cries, the diaphragm bulges. Infants with the type 3 abnormality frequently present only a dimple in the normal location of the anus. When the dimple is absent, scratching of the perianal skin or pinching it will usually cause puckering, indicating the existence of an external anal sphincter which is almost always present. Type 4 patients have a normal anus, and it is only by rectal examination that the complete obstruction which is within reach of the finger can be detected.

When fistulas are present the findings are characteristic. Rectoperineal fistulas are usually located between the usual site of the anal orifice and the scrotum or vagina and are detected by local examination. Rectovaginal fistulas are suspected when feces are seen coming from the vagina and the presence of these communications is confirmed by digital vaginal examination and by examination using a nasal speculum. The passage of meconium or flatus through the urethra indicates a rectovesical or rectourethral fistula, and *repeated* urinalyses should be done in all cases to rule out this type of connection.

It is *most* important to obtain information about the distance between the rectal pouch and the perineum, since the type of treatment employed is in part dependent on this distance. Such information may be obtained by passing a probe through a rectoperineal or rectovaginal fistula and gently directing it against a finger held on the perineum.

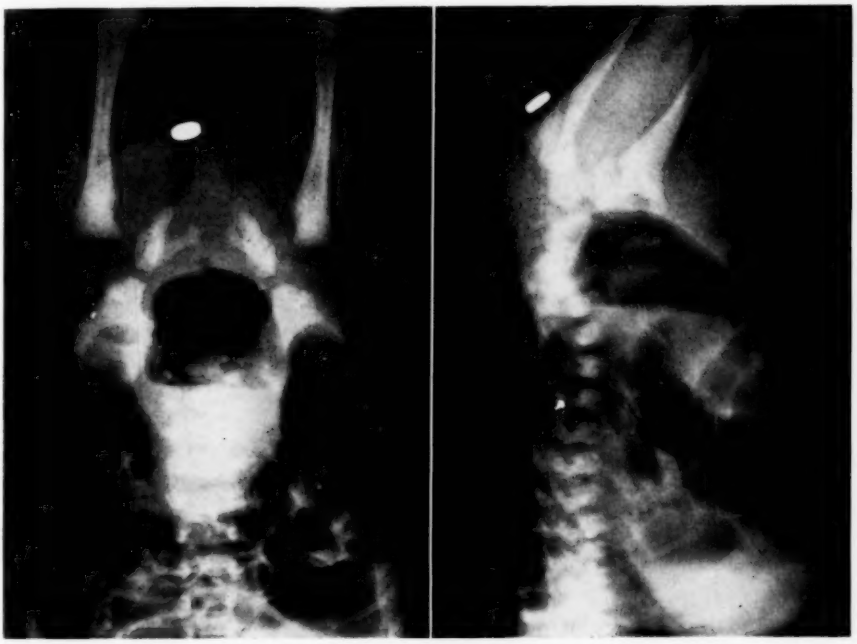

Fig. 4.—Anteroposterior and lateral roentgenograms of an infant with a type 3 anomaly, made with the infant inverted. Note the large distance between the gas-filled rectal pouch and the metal perineal marker. (From Rhoads, Pipes, and Randall: Ann. Surg., March, 1948.)

The most useful guide to the level of the rectal pouch is the roentgenogram taken with the child inverted so that gas in the colon will rise to outline the rectum (Fig. 4).[16] By placing a metal marker on the perineum at the normal location of the anus, the distance between the out-

lined rectal pouch and the anal marker can readily be determined. Because the bowel of the newborn infant is sometimes not filled with gas until eighteen to twenty-four hours after birth, roentgenograms made during the first day of life may be inaccurate.[11, 17] However, anorectal malformations rarely present problems so urgent that therapy cannot be delayed until the second day when studies can be obtained. When error does occur in the interpretation of films it is always on the side of overestimating the distance between the end of the rectum and the perineum. This probably leads to a slight increase in the frequency with which the abdominoperineal approach is employed. However, since the distance does not influence the success of this operation, while it seriously influences the outcome of the perineal operation, the error is much less dangerous than it would be if it were to indicate a pouch lower than it actually was. Lateral films are more valid than anteroposterior ones because the pelvic curve of the intestine gives an erroneous impression of short distance when viewed only in the anteroposterior projection.[18] Both views should be obtained. The infant should be suspended with its head down for at least five minutes, and if possible for ten minutes, before the roentgenograms are made in order to assure maximum ascent of the gas to the tip of the rectal pouch.[18] Further, tucking the child's thighs against the abdomen may be helpful in forcing gas distally.[17]

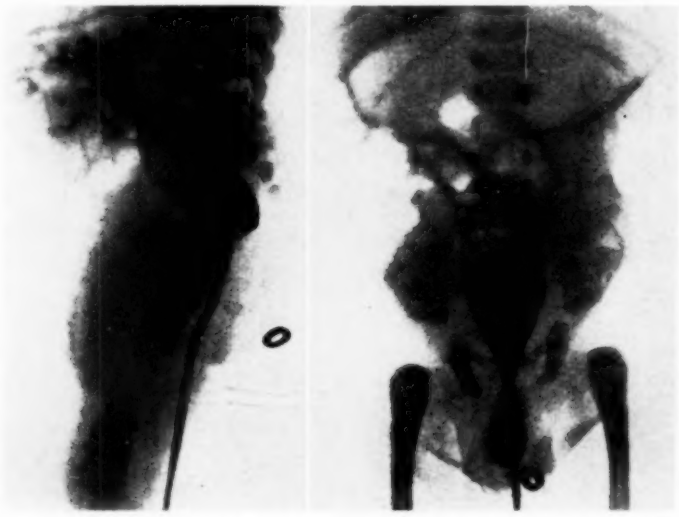

Fig. 5.—Lateral and anteroposterior roentgenograms of an infant with a type 3 anomaly, with Lipiodol outlining the rectal pouch. The Lipiodol has been injected through a catheter in a rectoperineal fistula. (From Arnheim: Am. J. Surg., May, 1951.)

Another helpful roentgenologic technique involves the utilization of rectoperineal and rectovaginal fistulas, when they exist, for the injection of radiopaque material (such as Lipiodol) to visualize the rectal

pouch (Fig. 5). Finally, if a colostomy has been done, instillation of thin barium into the distal loop may be of aid.

TREATMENT

The history of the treatment of malformations of the anus and rectum is not a particularly gratifying one to read. The past is distinguished by a lack of uniformity of approach associated with a long record of catastrophic results. However, in recent years great strides have been made in the therapy of these disorders so that now we are able to present a rational plan of management which can adequately handle each type of anorectal anomaly. This, combined with advances in pediatric anesthesia and in the preoperative and postoperative care of children has resulted in a great improvement in the results of treatment.

The type 1 malformation is the easiest to treat. Daily and later weekly dilatations of the anus, performed for a period of three months to one year, usually permanently overcome the difficulty. The greater part of the treatment can be performed by the mother at home. Failures in therapy are most often due to lack of persistence on the part of the mother or the physician, in which case the strictures recur. Infrequently the stenosed area must be excised and the rectum sewed to the skin. Table VII shows the good results of treatment reported by several authors.[6, 2, 3, 10, 11] The only factor which influenced the results adversely was death, which was almost always due to other anomalies.

Type 2 malformations are best treated by cruciate incision of the membrane followed by regular dilatations of the anus. Occasionally the entire membrane must be resected and the mucous membrane approximated to the skin. Table VIII shows the results of the definitive treatment of Type 2 malformations.[11, 3, 13, 6] Generally they are quite good.

TABLE VII. RESULTS OF DEFINITE TREATMENT (TYPE 1)

AUTHOR	NO. CASES	RESULTS (PER CENT)			
		GOOD TO SATISFACTORY	FAIR TO POOR	DEATH FROM ANORETAL DISEASE	DEATH FROM OTHER CAUSES
Ladd-Gross (1934)	20	90	0	0	10
Lu	9	77	0	11.5	11.5
Moore-Lawrence	4	75	0	0	25
Santulli	4	100	0	0	0
Mayo-Rice	4	100	0	0	0

Until recently, all type 3 deformities were treated by a proctoplasty using the perineal approach. An attempt was made to bring the rectal pouch down by dissecting through the infant's tiny perineum and then to suture it to the skin. If the pouch were low, the results were often successful. However, if the pouch were high, it was sutured to the skin under tension and it invariably retracted, leaving a scarred narrowed anus and an incontinent child. What is more, the extensive dissection required to bring the rectum down frequently impaired the perineal blood and nerve supplies and irreparably damaged the

sphincter. When the pouch was found to be so high that it could not be brought down, the perineal operation was concluded and a colostomy was done. More often than not, the child died. If the child survived, he was consigned to a miserable colostomy life, or he suffered subsequent unsuccessful attempts at repair of the defect. We have learned from experience that once an unsuccessful perineal operation has been performed, it is extremely difficult to achieve success by going back and trying again. In the past, fistulas were either treated at the time of the initial perineal proctoplasty, or subsequent procedures were performed to correct them. However, because visualization of the fistulas was often difficult in the small perineal wound, they frequently recurred.

Today, the perineal proctoplasty is performed only in instances when the rectal pouch is 1.5 cm. or less from the perineal skin as determined by the methods which I have previously described.[1, 19] The technique of the operation is as follows: With the infant in the lithotomy position and a catheter in the bladder, an anteroposterior incision is made in the midline extending from the scrotum or vagina backward. Some authors recommend dividing the external anal sphincter in half, while others advocate the division of only the anterior portions.[1, 9] Dissection is carried up to the rectal pouch, hugging the sacrum to avoid injury to the genitourinary tract. The rectal pouch is freed and is brought down between the halves of the external sphincter by the use of traction sutures making sure that it is under *minimal* tension. If a fistula is present it is divided, the anterior end is sutured closed, and the rectal end is exteriorized and resected. The sphincter is approximated around the rectum, and the pouch is anchored to the subcutaneous tissues. The pouch is then opened and evacuated, and the mucosa is approximated to the skin. Between one and two weeks after the operation, daily dilatations of the

TABLE VIII. RESULTS OF DEFINITIVE TREATMENT (TYPE 2)

AUTHOR	NO. CASES	RESULTS (PER CENT)			
		GOOD TO SATISFACTORY	FAIR TO POOR	DEATH FROM ANORECTAL DISEASE	DEATH FROM OTHER CAUSES
Mayo-Rice	62	52	45	3	0
Moore-Lawrence	19	73	16	0	11
Norris et al.	13	85	0	7.5	7.5
Ladd-Gross (1934)	6	83	0	17	0

TABLE IX. RESULTS OF PERINEAL PROCTOPLASTY IN TYPE 3 CASES

AUTHOR	NO. CASES	RESULTS (PER CENT)			
		GOOD TO SATISFACTORY	FAIR TO POOR	TOO EARLY TO EVALUATE	DIED
		Unselected Cases			
Moore-Lawrence	34	9	44	0	47
		Selected Cases			
Santulli	29	62	7	31	0

anus are started for a short time, usually not longer than several weeks.

Table IX shows the results of perineal proctoplasty in the treatment of type 3 malformations. When the operation was employed in unselected cases with no consideration given to the height of the rectal pouch, the results were poor and the mortality rate was high.[3] However, if the cases were carefully selected for the operation on the basis of a low rectal pouch, the results were good. Santulli[10] reported 62 per cent good results, while in 31 per cent of his patients a sufficient length of time had not elapsed to permit evaluation. He had no deaths, but this is partly due to the fact that his series is a recent one (1948 to 1951). Antibiotics and a greater knowledge of the care of these infants have been available to him from the start while the other authors have not been so fortunate.

When the rectum ends more than 1.5 cm. above the perineum, the abdominoperineal "pull-through" operation is the treatment of choice.[1, 19] Rhoads and associates[20] called attention to this procedure in 1948, since which time it has been employed with increasing success. In fact, the results have been so encouraging that some authors recommend it in all early type 3 cases, regardless of how low the rectal pouch is.[3, 13] The advantages of the operation are that all rectal pouches, no matter how high, can be adequately mobilized, and that fistulas can be easily visualized and closed. Previously unrecognized fistulas are readily seen in this approach. Moreover, extensive perineal dissection and sphincter destruction are obviated. No doubt, the procedure is more extensive than the perineal proctoplasty but the results appear to justify the greater hazard.

The technique of the operation is as follows: The patient is placed in the supine position with the left leg or both legs in the operative field so that both the abdomen and perineum may be approached. A catheter is inserted in the bladder. A left paramedian or transverse left lower quadrant incision may be used. The rectosigmoid is freed, and any fistula is divided. The anterior end of the fistula is sutured closed, although some authors recommend leaving it open and performing a suprapubic cystostomy when a rectovesical fistula is present.[1] A pelvic tunnel is created down to the perineum by blunt dissection. With the abdomen still open, a small anteroposterior incision is made over the anal dimple and a hemostat is passed upward by blunt dissection until a through-and-through canal exists. The rectum is pulled down through the canal until several centimeters protrude externally in order to obviate the dangers of subsequent contraction and sloughing of the tip. The peritoneal floor is repaired, the abdomen is closed, and the rectum is anchored to the perianal tissues and then opened. Seven to ten days later, the excess of mucosa is trimmed and the mucosa is approximated to the skin. Daily dilatations of the anus are started between one and two weeks postoperatively and are continued for several weeks.

The results of the abdominoperineal operation in the treatment of type 3 anomalies are shown in Table X.[1, 10] Since a number of the patients are too young to permit evaluation, the results in these cases are listed as "un-

determined." In the main, the results are very encouraging and few patients have had a poor outcome. Koop[21] has reported that only two of twenty-three patients followed for a three-year period have fecal incontinence. Fistulas which have been a troubling problem in the past have usually been eliminated completely. Finally, the mortality rate has been low, proving that today infants can well tolerate major surgery.

Colostomy still has a place in the treatment of imperforate anus.[19] When the child weighs less than 5 pounds or has a severe associated illness, colostomy is the procedure of choice, if intestinal obstruction is present. The abdominoperineal repair can then be done at a later time. When the infant has had an obstruction for too long a period, is dehydrated and toxic, and has a huge dilated bowel, colostomy is the safest measure to use. Finally, when the physician is hampered by lack of experience with these cases, or by poor anesthesia, the child's interests are best served by a colostomy. Today, with antibiotics and an increasing knowledge of the physiology of infancy, colostomy is a fairly safe procedure and is, in fact, well tolerated by most infants. It is important to make the opening in the transverse rather than in the sigmoid colon in order not to interfere with subsequent mobilization of the sigmoid and rectum in the performance of the "pull-through" operation.[19] A word of caution should be mentioned about the difficulties which develop with the distal loop of the colostomy. Mayo and Rice[11] and Moore and Lawrence[3] have reported a large number of cases in which the patients developed "distal-loop trouble," particularly fecal impactions and prolapse. Therefore it is recommended that the distal loop be completely separated from the proximal loop of the colon.

The question of when to operate frequently arises. If the infant has a complete obstruction or has a fistula between the rectum and urinary tract, as often occurs in the male, operation should be done immediately. During the first few days of life infants withstand operations well, and what is more, the bowel contents are sterile. If obstruction is not present as a result of decompression through a rectoperineal or rectovaginal fistula, operation may be delayed until about 3 months of age,[19] although some men recommend immediate operation in these cases also. When delay is too long the anxiety of the parents becomes marked, the danger of blockage of the fistula with its attendant morbidity increases, the child sometimes develops a greatly dilated bowel, and perhaps the external anal sphincter undergoes atrophy. If

TABLE X. RESULTS OF ABDOMINOPERINEAL OPERATION IN TYPE 3 CASES

AUTHOR	NO. CASES	BOWEL STATUS (%)			URINARY STATUS (%)		DEATHS (%)
		GOOD TO SATISFACTORY	FAIR TO POOR	UNDETERMINED	NORMAL	ABNORMAL	
Gross	77	52	20	23	81	14	5
Santulli	24	67	12	21	—	—	0

treatment is not given until after the child becomes of school age, as has been recommended frequently in the past, his psychologic and social growth may be permanently stunted.

Finally, a word should be said about dilatation of fistulas. The indications for dilatation of a rectovaginal or rectoperineal fistula are similar to the indications for performance of a colostomy in the patient with an obstruction. These are underweight, presence of severe associated disease, or the physician's lack of experience or proper facilities. It must be remembered that when fistulas have been dilated, they are more difficult to close later.

In patients with a type 4 malformation attempts have been made to do an oblique anastomosis of the upper and lower rectal pouches, but the operation is difficult and the results have been discouraging.[1, 22] As a result, the abdominoperineal "pull-through" is being used, the lower rectal pouch being excised and the upper pouch being brought down and sutured to the skin. Fortunately, this type of case is not frequent.

MORTALITY

The over-all mortality rate in malformations of the anus and rectum has been greatly reduced in recent years (Table XI). Early investigators had a mortality rate as high as 42 per cent.[3] Often, associated anomalies have caused as many deaths as the anorectal disease. The unusually low mortality rate of Mayo and Rice may in part be accounted for by the fact that many of their patients were older children and adults.[11]

Recently, as a result of advances in the treatment of congenital anorectal abnormalities, as well as in the treatment of associated anomalies, the mortality rate is no longer overwhelming. The report of Santulli[10] and the recent report of Gross[1] show mortality rates of only 6.4 and 8.6 per cent, respectively.

TABLE XI. OVER-ALL MORTALITY IN ANORECTAL MALFORMATIONS

AUTHOR	NO. CASES	DEATHS DUE TO ANORECTAL DISEASE (PER CENT)	DEATHS DUE TO OTHER ANOMALIES (PER CENT)	TOTAL MORTALITY (PER CENT)
Ladd-Gross (1908-1932)	162	19	7	26
Mayo-Rice (1910-1947)	165	6.6	2.4	9.1
More-Lawrence (1926-1951)	120	23	19	42
Lu (1927-1950)	74	30	3	32
Norris et al. (1948)	59	19	15	34
Bacon-Herring (1948)	98	11	0	11
Santulli (1948-1951)	62	0	6	6
Gross (1949-1951)	104	3	6	9

SUMMARY

The embryology of the anus and rectum has been reviewed in order to

understand how abnormalities in development produce the four types of anorectal malformations and associated fistulas with the genitourinary tract and perineum. About three-fourths of these cases have the type 3 defect and this type is the one which most often has an associated fistula. As regards fistulas, there is a distinct difference between male and female cases; the male usually has a communication with the urinary tract, while the female most often has a less serious rectovaginal connection. The incidence of associated congenital anomalies which are themselves frequently lethal is high, and investigations of the urinary and upper gastrointestinal tracts should be routine measures.

Infants with anorectal abnormalities may manifest the symptoms of complete intestinal obstruction, of partial obstruction, of difficulty in defecation, or may be asymptomatic, depending on the type of anomaly and the presence or absence of a functioning fistula. The diagnosis is readily made from the history and physical examination, and the level of the rectal pouch is best determined from roentgenograms made with the child inverted, from injection of accessible fistulas with radiopaque materials, and from probing of the fistulous tracts.

A plan of management for each type of malformation has been presented. The type 1 defect is treated by repeated dilatations and the type 2 cases receive incision and dilatations, both with good results. I have discussed the treatment of the type 3 anomaly in detail and have emphasized that the perineal proctoplasty is indicated only when the distance between the rectal pouch and perineum is 1.5 cm. or less. All other type 3 patients as well as type 4 patients should be treated by the abdominoperineal "pull-through" operation, a procedure which allows mobilization of any rectal pouch, visualization and closure of any fistula and at the same time does not destroy the external anal sphincter. The results of this operation are encouraging, but in inexperienced hands or when the child is in poor condition, performance of a colostomy or dilatation of a fistula is far safer. Definitive treatment should be given these infants early in life in order to avoid subsequent complications.

Finally, we have learned that better operative techniques, safer anesthesia, and greater knowledge of the care of young patients have combined to reduce the previously overwhelming mortality rate to less than 10 per cent. We need no longer expect every other patient with imperforate anus to die.

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ADRENAL INSUFFICIENCY IN INFANCY

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ADRENOGENITAL syndrome with adrenal insufficiency in young infants has been reported previously. Persistent vomiting and rapid dehydration, without apparent reasons, may suggest this disease. The knowledge of previous familial occurrence and the presence of intersexuality are of considerable help in the early recognition of this congenital adrenal abnormality. This additional case report is of a female pseudohermaphrodite who developed adrenal insufficiency in early life and has been followed for eighteen months.

CASE REPORT

R. S., a 5-week-old white infant of undetermined sex, was admitted to the Brooklyn Methodist Hospital, New York City, on Sept. 2, 1952, because of progressive feeding difficulty, vomiting, and loss of weight. The infant was born on July 28, 1952, spontaneously at term, the fourth child of apparently healthy parents. The birth weight was 7 pounds 2 ounces. Two weeks later the infant became weak and listless. The appetite decreased, and vomiting, which occasionally was projectile, occurred during or after each feeding. The vomitus contained milk only. There was no history of fever or diarrhea.

The parents and two siblings are alive and well. A third sibling died of persistent vomiting and loss of weight at the age of 11 weeks in another hospital. A post-mortem examination was reported by Dr. J. A. DeVeer,† which pointed to a probable adrenal insufficiency.

On admission the infant was markedly dehydrated, undernourished, and in a state of shock. The body weight was 5 pounds 5 ounces (Fig. 1). The skin was mottled but free from pigmentation or jaundice. The skeletal system was well developed. The measurements were: head 13.5 inches, chest 12.5 inches, and total length 21 inches. There were no abnormalities of head, neck, or chest. The abdomen was slightly distended. Peristaltic waves were seen occasionally. There was no pyloric tumor mass. The genitals resembled those of a male with hypospadias (Fig. 2). There was a long phallus measuring 2.5 by 1.3 cm. with a slitlike opening on the ventral side. Below the phallus there were two prominences of wrinkled skin partially fused in the midline which was never observed to be elevated during voiding. Gonads were not palpable.

Laboratory Data.—Hemoglobin ranged from 12 to 16 Gm. per 100 c.c. white blood cells from 8,000 to 13,000. Repeated urinalyses were normal. The blood electrolyte determination varied a great deal in different stages of the disease. During crisis, sodium and chloride were comparatively low and potassium was elevated. Sodium ranged from 130 to 142 meq., chloride from 88.2 to 104 meq., and potassium from 4.5 to 7.4 meq. Blood urea nitrogen varied from 7 to 21 mg. per cent, and blood sugar from 59 to 110 mg. per cent. The 17-ketosteroids output was definitely higher than normal in that age group. It varied directly with the dosage of cortisone which is shown in Table I.

The circulating eosinophil studies (Thorn test) showed only a partial

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Fig. 1.

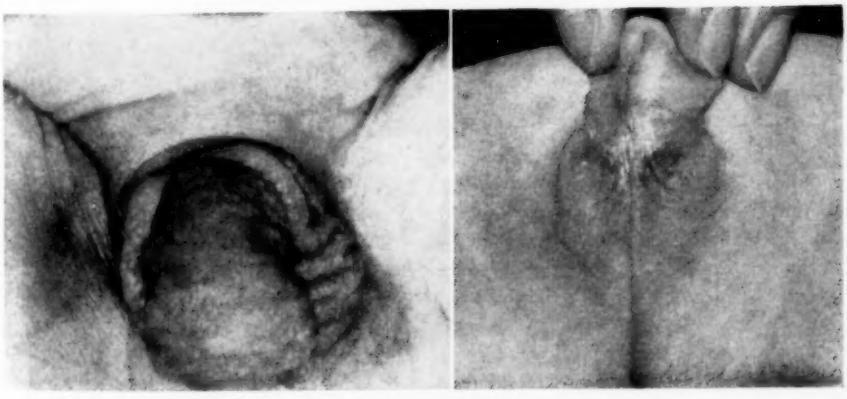

Fig. 2.

TABLE I. 17-KETOSTEROIDS (VARIATIONS WITH DOSAGE OF CORTISONE)

AGE (MO.)	17-KETOSTEROIDS MG./DAY	CORTISONE MG./DAY	THERAPEUTIC DAYS
5	3.1	20 mg. IM	7
13	16.2	Off cortisone for 2 mo.	--
13½	5.3	25 mg. P.O.	10
13¾	4.4	25 mg. P.O.	20
14	2.5	37.5 mg. P.O.	7

response to ACTH and Adrenalin which are shown in Table II.

TABLE II. CIRCULATING EOSINOPHIL STUDIES (AT 2 MONTHS OF AGE)

Initial eosinophil count	1,768 per cu. mm.
Following epinephrine test	1,200 per cu. mm.
Following ACTH test	968 per cu. mm.

Clinical Course.—On the first day of admission incubator and oxygen were necessary because of the subnormal temperature and cyanosis. Clysis of normal saline was started and followed by plasma intravenously. Adrenal cortical extract (Eschatin) was given up to 12 c.c. (0.2 mg. per cubic centimeter) intramuscularly within twenty-four hours. Thirty-six hours later the infant became alert and was able to take the formula slowly without vomiting. Three days later hydration was maintained without parenteral fluids.

It was decided to reduce gradually the adrenal cortical extract to ascertain what degree of adrenal insufficiency existed. On the tenth hospital day the hormone was reduced to 1 c.c. every eight hours. The patient became listless and began to spit up. The weight gain ceased. On the nineteenth hospital day the hormone was discontinued completely. Vomiting then ensued and soon almost complete collapse occurred. The hormone therapy was resumed but only in a low dosage (1 c.c. every twelve hours). One gram of sodium chloride was added to the daily formula. There was again a noticeable improvement in appetite and vitality but weight gain was slow. On the twenty-ninth hospital day the hormone was discontinued and sodium chloride was administered. The infant became lethargic, appetite decreased, and vomiting recurred.

Desoxycorticosterone (DCA) was started on the thirty-first hospital day with a dose of 1 c.c. (5 mg.) daily intramuscularly, in addition to the 1 Gm. of sodium chloride. The patient responded to this regime very well. DCA was reduced gradually in order to determine the minimal daily requirement. It was found that 0.5 c.c. (2.5 mg.) daily plus 1 Gm. of sodium chloride gives the best response. The subcutaneous implantation of three 75 mg. Cortate pellets was done, which equals 3 mg. daily dosage by injection. The infant was also maintained on 1 Gm. of sodium chloride in the daily formula. There was dramatic improvement following the implantation of the Cortate pellets.

The hospital stay was prolonged for two weeks because of upper respiratory infection. The infant was discharged on Nov. 8, 1952, in good condition, weighing 7 pounds 10 ounces.

The patient was readmitted to the Brooklyn Methodist Hospital on Dec. 6, 1952, because of gastroenteritis and dehydration. The condition was improved rapidly by the parenteral administration of glucose, saline, and antibiotics. A short course of cortisone

(25 mg. intramuscularly for five days) was given because of the persisting hypoglycemia and hirsutism. A cystogram was done which revealed no indication of a genitourinary sinus. The infant was discharged on Dec. 17, 1952, in good condition, weighing 10 pounds (Fig. 3). Continuous cortisone therapy was advised with a dosage of 12.5 mg. every day.

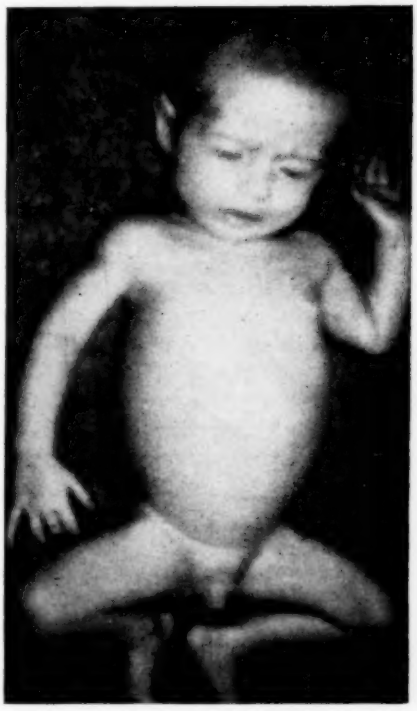

Fig. 3.

Fig. 4.

The patient was admitted to the Memorial Center, New York City, on Sept. 7, 1953 (Fig. 4) because of listlessness and vomiting for three days. The mother stated that the patient had not received cortisone for two months. On admission she appeared lethargic and dehydrated. Blood pressure was 90/40 mm. Hg. Physical examination was essentially negative except for hypotonicity of the extremities. There were no signs of focal infection. The patient was treated with saline intravenously and adrenal cortical extract intramuscularly (2.5 mg.). Cortisone therapy was delayed for twenty-four hours because a urine specimen was being collected for 17-ketosteroid. It was started with 25 mg. daily in divided dosage. Three weeks later cortisone was increased to 37.5 mg. daily in order to depress the 17-ketosteroid output (Table I). The cystogram was repeated and again failed to demonstrate the genitourinary sinus. Laparotomy was performed in October

and complete female organs were found. There was no evidence of any male organs. The patient was discharged on Oct. 23, 1953, in good condition. Continuous cortisone therapy was again advised with a dosage of 25 mg. daily in divided dosage.

COMMENT

This patient was born with an enlarged clitoris which may indicate prenatal adrenocortical hyperplasia.

Adrenal insufficiency in infancy may reach an irreversible crisis in a short period if the diagnosis and substitution therapy are not carried out properly and promptly. The diagnosis may be made from the clinical symptoms, laboratory findings, previous family history, or the signs of intersexuality. Deamer and Silver[1] pointed out that, in contradistinction to adults, the pigmentation of the skin and mucous membrane is not a prominent finding in infants. Therefore, this could not be depended upon as a diagnostic aid.

The control of the virilism in the female pseudohermaphrodites caused by the adrenal hyperplasia has been studied extensively by Wilkins and his associates.[2, 3, 4] Partial adrenalectomy and administration of estrogen or other medications in order to reduce the overproduction of androgen were utilized before the use of cortisone. The major action of the cortisone is to suppress the secretion of the abnormal pattern of adrenal hormones. The amount of cortisone therapy could be adjusted by the 17-ketosteroid excretion. Table I shows that 17-ketosteroids vary directly with the dosage of cortisone.

Wilkins believes that after implantation of Cortate pellets they become encapsulated and the absorption is slowed, and the patient may need extra sodium chloride intake. In this case additional hormone and sodium chloride were necessary during infection.

SUMMARY

1. An additional case of adrenogenital syndrome with adrenal insufficiency of a female pseudohermaphrodite at the age of 5 weeks is reported.

2. Early diagnosis and prompt therapy probably averted the death of the infant.

3. Adrenal insufficiency was confirmed by the laboratory findings as well as by the subsequent improvement on a trial of hormone therapy.

4. Hirsutism and elevated 17-ketosteroids were controlled after the administration of cortisone.

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Medical Progress

GASTROINTESTINAL ALLERGY IN INFANCY

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GASTROINTESTINAL allergy is defined as allergy involving the gastrointestinal tract whether due to foods, inhalants, pollens, molds, or drugs. Most commonly the allergen is a food, but gastrointestinal allergy must be differentiated from food allergy which is allergy due to a food whether manifested by symptoms in the gastrointestinal tract or elsewhere in the body.

CLINICAL SYNDROMES

The clinical syndromes which may be seen in infants as a result of gastrointestinal allergy include vomiting, diarrhea, celiac syndrome, mucous stools, colic, abdominal pain both acute and chronic, intestinal bleeding, cheilitis, canker sores, angioneurotic edema of the lips, palate, and other parts of the gastrointestinal tract, anorexia, and constipation. All of these conditions are very common in infants and their incidence due to allergy is difficult to assess because there are so many other possible causes. Rowe[42] believes that gastrointestinal allergy is much more common than is usually appreciated, especially in infancy and childhood, when it is often responsible for colic, pylorospasm, nausea, vomiting, regurgitation, mucous stools, constipation, and other general symptoms. Hill,[38] on the other hand, while recognizing that severe symptoms such as vomiting and diarrhea may be the result of food sensitivity, believes that colic, chronic vomiting, diarrhea, malnutrition, and pylorospasm are caused only occasionally by allergy. Andresen,[3] in a discussion of patients of all ages, states that nearly 20 per cent of patients with gastrointestinal complaints have some allergic reactions and that in 11 per cent the principal symptoms are definitely allergic in origin. Clein[8] in a study of 140 infants, all of whom were allergic to cow's milk, found pylorospasm with regurgitation and vomiting in 39 per cent, colic in 29 per cent, diarrhea in 24 per cent, mucus in the stools in 6 per cent, blood in the stools in 5 per cent, chronic constipation in 5 per cent, and anorexia with refusal of milk in 4 per cent. In another study[9] of 100 allergic children followed from birth to 10 years of age, vomiting or pylorospasm occurred in thirty-six, and colic, excessive gas, recurrent diarrhea, or constipation in twenty-three. Abdominal pain was the most common symptom referable to the gastrointestinal tract. Cyclic vomiting was a serious problem in two. Canker sores were common.

While these reports give some indication of the importance of gastrointestinal allergy in infancy, there is no report giving a clear picture of the actual incidence of these syndromes in the general infant population. A knowledge of the general incidence as

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well as the symptomatology of gastrointestinal allergy would be very helpful to the practicing pediatrician in diagnosing this condition. Fontana,[16] Ingelfinger and associates,[23] and Withers[34] have written excellent reviews on the subject of gastrointestinal allergy.

Vomiting.—Many authors have reported vomiting as a result of gastrointestinal allergy. Schloss[44] noted that vomiting and diarrhea developed in some infants when small amounts of cow's milk were fed, but that in some the symptoms did not occur when the milk was thoroughly boiled before it was fed. Some of the infants showed positive intracutaneous tests with milk. Stafford and co-workers,[48] McCarthy and Wiseman,[29] and Glaser[35] have also reported vomiting due to gastrointestinal allergy. Rowe[41] believes that it is a fairly frequent manifestation in young infants and children. Rosenblum and Rosenblum[39] found vomiting as a minfestation in 47 per cent of sixty infants with gastrointestinal allergy. The onset was generally in the newborn period and cow's milk was the most frequent offender. Clein[8] also found vomiting in 39 per cent of 140 infants sensitive to cow's milk.

Fries and Jennings[18] believe that hypersensitivity to food is one cause of recurrent or cyclic vomiting and report a case in an infant to support this view. Rowe[42] believes that it is frequently due to food allergy. Hill,[38] on the other hand, does not believe that cyclic vomiting has anything to do with food allergy.

Opinions concerning allergy in pylorie stenosis are also conflicting. Glaser[35] believes the evidence is in favor of this syndrome having an allergic basis as do Cohen and Breitbart[10] and Balyeat and Pounders.[5] Rowe[42] believes that the role of allergy in this condition is questionable.

Celiac Syndrome.—Many cases of celiac syndrome have been described in which the etiological factor is food allergy, and it is now the concensus that allergy must be considered as one subdivision of the celiac syndrome.

Andersen and di Sant' Agnese[1] state that occasional cases of celiac syndrome are due to gastrointestinal allergy but that there is little evidence for allergy in the majority of celiac patients. Kunstadter,[24] as early as 1942, reported three cases of typical celiac syndrome due to gastrointestinal allergy to milk and other foods, and since then, many other reports have been published by McKhann and associates,[31] Lapin,[26] Block[7] (many foods, especially cow's milk), Dicke[11] (wheat and rye flour), McCreary and coworkers,[30] Clein[8] (milk), Anderson and associates[2] (wheat), and Kunstadter and Shultz[25] (milk). None of these authors, however, claims that gastrointestinal allergy is anywhere near the most common cause of the celiac syndrome but rather that it is occasionally a cause and therefore must be considered in the treatment of all cases, especially those which do not respond to the conventional methods of therapy.

Diarrhea Other Than the Celiac Syndrome.—Many authors have reported diarrhea as a manifestation of gastrointestinal allergy in infants without the clinical picture of the celiac syndrome. Schloss[44] noted diarrhea in infants following the ingestion of cow's milk. Rowe[41] feels that diarrhea in young infants and children is not infrequently due to food allergy.

Rosenblum and Rosenblum[39] found diarrhea as a manifestation in 83 per cent of sixty infants with gastrointestinal allergy. In the majority the diarrhea began in the first few months of life, in 35 per cent after the third month, and in a few after the first year. Cow's milk was the most common offender. Lapin and Weissberg[27] described infants with allergic colitis who had no or slow weight gain associated with chronic or recurrent diarrhea. They were relatively well nourished and did not show the clinical picture of celiac disease. They responded to withdrawal of certain foods from the diet, and cow's milk was a common offender. Clein[8] found diarrhea in 24 per cent of 140 infants sensitive to cow's milk. Hill[38] believes that diarrhea in infants is only occasionally caused by allergy. Wergeland[52] reported three cases of probable allergy to human milk, all of which were characterized by profuse diarrhea. Rothman[40] has written a review on diarrhea of allergic origin.

Mucous Stools.—In a study of 140 infants suffering from cow's milk allergy Clein[8] found that 6 per cent passed considerable mucus in their stools. These also suffered from diarrhea, but most of the other infants in the study with diarrhea did not pass visible mucus in the stools. Rowe[42] believes that gastrointestinal allergy in infancy and childhood frequently causes mucous stools.

Colic.—Rosenblum and Rosenblum[39] described colic as a manifestation in 45 per cent of sixty infants with gastrointestinal allergy. The colic had its onset early in life in the majority of cases, and cow's milk was the most common offender. Donnally,[12] Peterman,[33] Glaser,[35] Stafford and associates,[48] Rowe, [41, 42] and Clein[8] consider colic to be an allergic manifestation in many cases. Donnally, Stafford, and Rowe point out that in early infancy, colic may be caused not only by cow's milk and other foods, but by substances eliminated in the mother's milk, and believe that cow's milk is a comparatively frequent offender. Glaser states that not all colic is of allergic origin but the severer cases often are. In proportion, as the infant suffers from colic, so may subsequent manifestations of allergy appear in later infancy and childhood. He lists the presumptive evidence that colic is of allergic origin as follows: (1) There is a definite incubation period of ten days to three weeks after birth before colic develops. (2) During the first weeks of life transient positive reactions to cutaneous tests occur which disappear as the child becomes accustomed to the new foods.[13] (3) Transient precipitins also occur in the blood stream to these allergens during the same period.[45] (4) Transient eosinophilia appears as new foods are introduced and disappears as the child becomes accustomed to these foods.[6] (5) Infants who have had colic have eczema more frequently than infants who have not had colic.[53] The specific evidence is the response to changes in diet. Hill,[38] on the other hand, believes that colic is only occasionally caused by allergy.

From this review it appears that the treatment of colic must, therefore, include the removal of the possible allergenic agents from the infant's diet or from the mother's diet in the case of the breast-fed infant. This is the only way in which the etiology can be definitely established in a given patient.

Chronic Abdominal Pain Other Than Colic.—Schloss[44] was one of the first to place certain cases of abdominal pain in the category of gastrointestinal allergy. Both Peterman[33] and Hill[38] state that allergy is one cause of abdominal pain though Hill does not consider this to be common. One of the most impressive reports descriptive of this syndrome is presented by Ratner.[37] He observed a pair of twin infants in whom symptoms developed after the ingestion of raw milk. Urticaria developed in one twin, and abdominal pain, vomiting, and diarrhea in the other. Only the former showed positive skin tests with milk. Ratner points out that abdominal pain may appear alone or accompany an acute attack of urticaria or asthma. Recurrent abdominal pain is usually associated with other dermal or respiratory allergic manifestations. Often one or more of diarrhea, flatulence, mucous stools, nausea, vomiting, or constipation are present also and the ingestion of a particular food results in these symptoms. Fever or localized tenderness may be present but are usually absent.

Acute Abdominal Pain.—Many cases of acute abdominal pain simulating surgical conditions but due to allergy have been reported. Most of these have occurred later than infancy but the same principles apply to the infant. As Ratner[37] points out, the abdominal pain is initiated by spasm of the gastrointestinal smooth muscle, wheal formation in the gastrointestinal wall, spasm of the small vessels of the gastrointestinal wall, or a combination of these factors. Ratner also points out that due consideration to the following points favoring allergy must be given in the differential diagnosis of the surgical abdomen: (a) a previous history of gastrointestinal symptoms or food sensitivities; (b) a history of other forms of allergy; (c) the presence of eosinophilia; (d) severe abdominal pain with physical signs that are atypical or negative. However, the pathology, even though initiated by allergy, may become irreversible and actually lead to a surgical condition so that if the signs point to appendicitis or intussusception, surgical intervention is necessary in any case. Sneierson and Mazar[47] and Duke[14] also stress the importance of including allergy in the differential diagnosis of the acute abdomen. Sneierson and Mazar stress that if, at the time of laparotomy, the pathological condition of the intestine appears to be reversible and the diagnosis is allergy, resection should not be done.

Gastrointestinal Bleeding.—Rubin[43] reported six newborn infants with allergic intestinal bleeding. In each of them, cow's milk was started immediately or within a few days after birth. About three weeks later colic appeared and became progressively worse. Loose stools began a few days after the onset of the colic, and mucus and bright red blood, sometimes amounting to profuse hemorrhage, appeared in the stools. In each case there was prompt and complete disappearance of the blood from the stools within forty-eight hours after withdrawal of cow's milk from the diet. The mucus in the stools and the colic disappeared shortly afterward. Donnally[12] and Rowe[41, 42] also state that food allergy may cause intestinal bleeding in infants. Rowe claims that this results from increased permeability of the capillaries of the intestinal mucosa. Clein[8] describes

blood in the stools in 5 per cent of 140 infants sensitive to cow's milk.

Miscellaneous.—Canker sores are frequently considered to be due to allergy and Rowe[42] claims that they are usually due to food allergy. Anorexia, according to Rowe,[42] often is relieved by the elimination of allergenic foods. Clein[8] reported five infants who refused to eat when on a cow's milk formula, but ate readily when given soy milk. When the cow's milk formula was substituted, they again refused to eat.

Clein,[8] in a study of 140 infants allergic to cow's milk, found seven, or 5 per cent, who suffered chronic constipation as a manifestation of their allergy.

DIAGNOSIS OF GASTROINTESTINAL ALLERGY

General Remarks.—There are many difficulties in the diagnosis of gastrointestinal allergy. All the manifestations of gastrointestinal allergy are caused by a great many other diseases both organic and functional and, therefore, it is only by careful study of a given patient that a correct diagnosis can be arrived at. The history is important since a careful history may point to foods causing the symptoms. The association of other allergies in the patient or in members of the patient's family may also point to the diagnosis. The relation of symptoms to ingestion of foods, which are the commonest cause of gastrointestinal allergy, may also be helped by a food diary. History may point to inhalants, pollens, molds, or drugs as etiological agents. Physical examination is usually negative except in such diseases as celiac syndrome where there are characteristic physical findings.

Dietary Manipulation.—One of the most common means of confirming a diagnosis of gastrointestinal allergy is removing the suspected food from the diet. If the diagnosis is correct there is subsequent clearing of symptoms followed by return of the symptoms when the food is put back in the diet. Other methods include the use of elimination diets,[42] denatured diets,[37, 38] and test diets.[4] All of these methods are extremely useful in many cases.

Skin Tests.—There is general agreement that skin tests are of limited value in the investigation of gastrointestinal allergy. It is extremely common for clinically important foods to give negative skin reactions. However, there is fairly general agreement that, if the patient is not responding to treatment based on the other methods of diagnosis, it is worth while resorting to skin tests since they will sometimes give important leads which have been missed by the other diagnostic methods.

Gastrointestinal Eosinophilia.—Nance[32] reported more than thirty infants suffering from gastrointestinal allergy with such syndromes as projectile vomiting, diarrhea, colic, celiac disease, and fat intolerance, and in all of these he demonstrated eosinophils in the stools. He described in detail the technique for this examination. Rosenblum and Rosenblum[39] described sixty infants with gastrointestinal allergy, all of whom had eosinophils in the stool. Of seventy-six control infants, none had eosinophils in the stool. Block[7] made use of eosinophils in the stool to differentiate celiac syndrome due to gastrointestinal allergy from the other forms of celiac syndrome. Clein,[8] speaking of vomiting as a result of gastrointestinal allergy, states that mucus is frequently found in the vomitus and that this mucus frequently shows a marked eosinophilia.

Effect of Antihistaminics and Other Drugs.—Adrenalin, the antihistamines, and occasionally other drugs are often of value in the diagnosis of gastrointestinal allergy. Sheldon and associates[46] state that the effect of antihistamines has some diagnostic value if interpreted properly. Almost 50 per cent of patients with gastrointestinal allergy are benefited. However, some of the therapeutic effects of these drugs may be due to their atropine-like properties or sedative effects rather than to their antihistaminic activity; hence, for diagnostic significance the patient must be helped by antihistamines but not by belladonna and its related compounds or by sedatives. Sneierson and Mazar[47] also feel that both Adrenalin and the antihistamines are of value in the differential diagnosis of gastrointestinal symptoms. Lapin and Weissberg[27] claim that the antihistamines give palliative relief in allergic colitis. Ratner[37] states that epinephrine is the drug of choice for acute abdominal pain due to allergy, while atropine, belladonna, Syntropan, and sedatives may be used to treat or prevent recurrences.

X-ray Studies.—Many authors have reported x-ray studies in the diagnosis of gastrointestinal allergy. Many of these were done on children as well as on adults; no studies are reported entirely on infants but the same factors obviously apply to infants. All these studies consist of examining the patient by contrast medium with and without the suspected food allergen in the medium. Fries[17] and Fries and Mogil[19] studied thirty allergic children ranging in age from 4 to 14 years, all of whom suffered from nausea, vomiting, epigastric distress, or abdominal cramps within a few minutes of ingesting small amounts of offending foods. X-rays revealed pylorospasm resulting in gastric retention as the most constant finding. Increased small intestinal segmentation and colonic spasm were also observed but less frequently. In another study by Fries and Zizmor[20] on twelve children, the allergens were administered both orally and rectally. They observed peristaltic disturbances in the gastrointestinal tract manifested as gastric retention, increased or decreased motility of the gastrointestinal tract, and spasm or dilatation of the stomach or intestines. By means of similar studies, Tallant and associates[49] observed abnormalities of the small intestine, consisting of narrowing, segmentation, and scattering. Lepore and co-workers[28] observed marked disturbances of motility of the small intestine, and Eyermann[15] observed spasticity of the colon.

Gastroscopy.—Pollard and Stuart[34] state that the administration of a food allergen may result in definite gastroscopic changes consisting of hyperemia, edema and thickening of the rugal folds, diminished peristalsis, grayish mucus clinging to the mucosa, and submucosal hemorrhages. A control gastroscopy should be performed before administering the suspected food.

Sigmoidoscopy.—Sheldon and associates[46] claim that sigmoidoscopy presents no picture diagnostic of gastrointestinal allergy. However, Lapin and Weissberg[27] take the opposite view, claiming that sigmoidoscopy helps in the diagnosis of allergic colitis. In this condition the mucosa appears reddened, edematous, and covered with considerable mucus. This is important in differential diagnosis because a severe or poorly treated case of allergic

colitis may present a clinical picture of celiac syndrome. In both cystic fibrosis of the pancreas and nonallergic celiac disease, sigmoidoscopy presents a normal picture.

Concluding Remarks.—In the investigation of a patient by these diagnostic methods, it is important to use enough of the methods to make a definite diagnosis although they are never all needed in any one case. It is also very important to exclude other causes for the symptoms since it is just as bad to overdiagnose gastrointestinal allergy as to underdiagnose it. Each case must be considered on its own merits before a diagnosis is made.

DISCUSSION

The diagnosis of gastrointestinal allergy implies an antigen-antibody reaction with the antigen fixed somewhere in the gastrointestinal tract and the antibody entering the body, usually via the gastrointestinal tract in the form of food, but by any other route in the form of food, inhalant, pollen, mold, or drug. In the absence of skin tests which can be clinically correlated with the symptoms, it is obviously impossible to prove an antigen-antibody reaction in every patient in which the diagnosis is made. However, there are many reasons for thinking that such takes place. In the first place, there are many possible ways in which an infant may become sensitized to food, the commonest cause of gastrointestinal allergy in infants, thus paving the way for an antigen-antibody reaction to occur. These means of acquisition of food allergy have been enumerated by Ratner[38]: (1) sensitization in utero, (2) sensitization by breast milk, (3) occasional feedings of raw milk during the neonatal period, (4) raw foods taken during convalescence from disease, (5) fad diets, (6) overfeeding, and (7) excessive indulgence in seasonal or bizarre foods. Any of these, on occasion, may apply to an infant, and antibody may be formed in any portion of the gastrointestinal tract, which later becomes the shock organ. In addition, experimental work on human beings has demonstrated definitely that antigen-antibody reactions occur in the gastrointestinal tract. Walzer[50] reports studies on the passive sensitization of the mucous membrane of the human rectum. The antigen, administered either rectally or orally, resulted in a reaction at the sensitized site. Gray and associates[22] report similar studies on the human ileum and colon. Antigen administered orally, by introduction into any part of the bowel, or by direct application locally to the mucous membrane results in reactions at the sensitized sites. Fries and Zizmor[21] have reported thirty children with gastrointestinal allergy studied clinically by the oral or rectal administration of foods. By the oral administration of foods in thirty subjects they produced nausea in thirteen, vomiting in seven, abdominal pain in six, and oral and pharyngeal symptoms in two. By the rectal administration of foods in sixteen subjects, they produced abdominal pain in twelve, tenesmus in four, nausea in one, and a sense of fullness in the abdomen in one.

Experimental work on animals has gone further to demonstrate that antigen-antibody reactions can occur in the gastrointestinal tract. Walzer and associates[51] report passively sensitized sites in the mucous membrane of the gastrointestinal tract of monkeys, and in these they produced reactions at the site by injecting the antigen intrave-

nously or into the lumen of the bowel. Ratner[36] induced retching and vomiting in guinea pigs by feeding them milk three weeks after they had been sensitized to milk by forced milk feedings.

Thus, it has been demonstrated that there are many ways in which it is possible for the gastrointestinal tract of the infant to become sensitized, in other words, to have antibody fixed in it, and it has also been demonstrated experimentally, both in human beings and in animals, that antigen-antibody reactions can occur in the gastrointestinal tract. By analogy, it may be concluded that such an antigen-antibody reaction is taking place in the gastrointestinal tract of an infant in whom a diagnosis of gastrointestinal allergy is made if the following criteria are strictly observed: (1) The patient has a history compatible with a diagnosis of allergy. (2) A specific allergen, almost always a food in an infant, must be determined. (3) Symptoms come on within a reasonable time after ingestion of that food. This time is usually within a few hours but may be as long as a day or two in many cases and, as has been pointed out by Rowe,[42] it is possible in a few patients that the food or other allergens remain in the blood and body tissues for days or weeks and their persistence may cause recurrences or continuation of symptoms in certain patients for weeks after the allergenic foods have been completely removed from the diet. (4) Symptoms disappear within a reasonable time after exclusion of the food from the diet. This is usually within a day or two but, again, as has been reported by Rowe,[42] it may take days or even weeks in certain instances. (5) Symptoms return when the food is reintroduced into the diet. (6) The food is one that is commonly tolerated without difficulty by most people. This will exclude foods which frequently cause gastrointestinal irritation which has nothing to do with allergy. (7) The diagnosis is supported by other allergic manifestations to the same allergen, for example, urticaria. (8) The diagnosis is supported by other known allergies in the same patient. (9) The diagnosis is supported by positive findings in other special diagnostic procedures such as blood eosinophilia, gastrointestinal eosinophilia, positive x-ray findings compatible with allergy, gastric or sigmoidoscopic examination, the effects of drugs, and the results of skin tests.

TREATMENT OF GASTROINTESTINAL ALLERGY

The main treatment of gastrointestinal allergy is dietary control, that is, eliminating the food which is causing the reaction. It is very important in the infant to remember that an adequate diet must be provided, one that is complete in the infant's needs for calories, carbohydrate, protein, fat, minerals, and vitamins. Therefore, food substitutes, especially the milk substitutes, must be used for important foods that are removed from the diet. Some authorities favor oral hyposensitization with foods but the majority feel that this is of little or no value and that the food should be completely eliminated from the diet. Usually the patient will be able to eat that food again without difficulty in several months or a few years. If pollens, inhalants, or molds are implicated, the treatment is both avoidance by environmental correction and hyposensitiza-

tion by injection. In the case of drugs, their use must be avoided.

SUMMARY

Gastrointestinal allergy in infants has been described in terms of the clinical syndromes which occur, namely, vomiting, celiac syndrome, diarrhea, mucous stools, colic, abdominal pain, and intestinal bleeding. The different methods of diagnosis, the criteria of a definite diagnosis, and the treatment of these conditions have also been reviewed.

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Psychologic Aspects of Pediatrics

THE ADJUSTMENTS OF ADOLESCENTS TO POLIOMYELITIS

A Study of Six Patients

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MUCH has been written about the psychologic adjustment during the acute stage of poliomyelitis. Methods and manners of handling the individual have been extensively described. It is recognized that one of the worst features of poliomyelitis is a personality maladjustment which arises as a reaction to the physical handicaps. Levy[17] describes three stages in the usual response to a marked deformity: (1) immediate withdrawal, (2) absorption with self, and (3) gradual return to reality. He does not consider the time factor of each stage, but he does mention that the individual may be arrested at any level of the response. Whether the person remains withdrawn depends upon the severity of the residua, his personality, his family, and friends.

METHOD

In an attempt to understand the problems of personal, emotional, and situational adjustment to poliomyelitis, six young people and their parents were chosen for study. The cases were selected at random from the files of a large teaching hospital, a small special poliomyelitis ward in a hospital, and a rehabilitation hospital. The only criterion was that the patient had had poliomyelitis as an adolescent with paralytic residua, and that he be interviewed at least three years following the acute attack. The adolescent period was chosen since this is a difficult period of adjustment. It was felt that poliomyelitis, which strikes suddenly and has a prolonged period of rehabilitation, would influence normal psychologic development, and that changes would be most pronounced in adolescence, when emotional independence is emerging.

Criticism concerning the validity of answers to questions about reactions to situations several years before is justified. Certainly subjects are colored and changed constantly with each new experience and by reflection upon the past. Yet it seems that reactions may be considered significant if similarity is found in several cases.

Both the person who had poliomyelitis and his family were interviewed separately. The average individual interview was three to four hours. Similar questions were asked of the parents and of the poliomyelitis victim. They generally covered what were considered the four major problems: (1) the personality of the patient before the onset of poliomyelitis, (2) the psychologic reaction during the acute stage of poliomyelitis, (3) the psychologic alterations during the rehabilitation stage, and (4) the present attitudes toward the disease and toward life goals.

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TABLE I. SIGNIFICANT RESPONSES OF PATIENTS AND PARENTS TO POLIOMYELITIS

TOPICS	SALLY O+	NORMAN O→	EDWARD O→	KENNETH O→	NICHOLAS O→	NANCY O+
Age at onset (yr.)	17	17	18	18	18	13
Age at interview (yr.)	25	23	26	21	21	19
Type of polio	Bulbarspinal	Bulbarspinal	Bulbarspinal	Bulbarspinal	Bulbarspinal	Spinal
Personality prepolio	Good student. Studied piano, singing, wrote.	Excellent student; few sports. Social inferiority complex	Extrovert; very impatient with others; made own decisions at early age. Mother died when he was 4 years old	Fair in school, not interested in studies except math. Liked sports	Quiet, studious, educated in private Jesuit school. Interested in ideas, not people	Liked school; very active in sports; many girl friends
Self	Unathletic. Many girl friends; no boy friends					
Parents	Tender, sensitive, very smart. High scholastic standing	Shy, excellent student, determined to achieve goals	Stepmother: Self-centered, spoiled brat. Considered self "little tin god." Liked sports	Physically and emotionally immature: unable to accept authority, very combative	Good student; full of ideas, spirited childlike enthusiasm	Active in school and sports. Quiet, studious, ambitious, persistent
Immediate reaction	Happy to go to hospital; felt that she would be safe	Went to hospital with arms paralyzed but unafraid since mother had recovered completely from polio	Went to hospital knowing he had polio but was not afraid, felt Kenny technique would cure him	No immediate fear; thought of polio as "hitting your legs" and that he would be well in few days	Thought of polio poster and polio as "hitting your legs." Thought of recovery with limp. Told priest he would not die	Wanted to get to hospital; felt she would recover there. No fear of dying although given last rites
Self						
Parents	Terrified. Did not feel Sally would die, yet turned to Jewish customs for saving the dying	Anxious, but faith in recovery since mother had had polio at 6 yr. and recovered	Not afraid until end of first week when put in respirator, then anxious but no fear of dying	Knew son was very ill but no fear of death	Anxious, but faith in recovery gained through prayer	Sudden arm paralysis was "terrible blast." Faith in recovery by prayer

Acute illness Self	Felt excruciating pain but no concept of having polio for 5 or 6 wk. Felt sinful, thus atoned by being as good as possible	Extreme pain. Delerium intermittent for 5 mo. Realization of polio after 5 wk. Felt polio result of masturbation. Prayed for forgiveness	Petulant, demanding. Fear of dying. Dreams of being before judgment seat arguing for right to live	Extreme pain. Petulant, demanding, crying, easily upset	Unbelievable pain. Easily upset; demanding. Constant prayer	Easily upset, demanding. Constant prayer for ability to use hands again
Parents	Feeling of helplessness but not defeat. Torture in watching body wasting	Frightened because of prolonged paranoid delusions. Lived from day to day with determination that he should recover	Hoped that stepson would not live because of probable inability to accept crippling	Frightened because they felt son was being mismanaged. Determined to get best care; called in outside specialists	Never told son would die; never wanted to believe he would. Worked with nurse and boy friend to keep his spirit up	Terrified because told by a physician that city hospital was poor. Received help from National Foundation
Rehabilitation Self	Faith in physiotherapy. All attention focused on breathing, swallowing, possibility of living, mental alertness	Physiotherapist's faith in recovery. Concern about mental recovery	Fought against being removed from respirator; suddenly made up own mind to get out. Physiotherapist—her faith in you was key to success	Hates physiotherapists; has had more than ten. Each acts as though he only had a job to do	Apprehensive of ability to breathe. Encouraged by physiotherapist who promised slow constant gain	Faith in physiotherapist who spent extra time with Nancy stressing individual muscle concentration
Parents	Distressed in turning daughter over to physiotherapist, yet realized she was most important in recovery	Only faith in physiotherapist and selves. Felt it was important for son to come home and see friends	Faith in physiotherapists; felt physicians pessimists in decisions	Faith only in what they as parents can do; physiotherapists show no real interest	Physiotherapist constantly pushing son to do everything. Parents feel they must support this effort	Physiotherapist most important because of constant attention. Felt early contact with friends important
Early days posthospital Self	Looked at others with wonder at ease of walking, breathing. Easily tired; moved to tears. Noticed details of nature	Parents hovered over him. Immediately returned to college; helped by peers	Parents hovered over him. Wishing freedom of action, he returned to college and made good adjustment	Not yet permanently home from hospital; home on weekends and one 3-week period. Visited by friends at home	Felt better at home although confined to rocking bed 8 hr. a day. Began attending college in wheelchair	Return to school with fear of not being able to keep up. Constant fatigue; easy crying

TABLE I.—CONT'D

TOPICS	SALLY O+	NORMAN O→	EDWARD O→	KENNETH O→	NICHOLAS O→	NANCY O+
Parents	Worried whether Sally would make good social adjustment. People avoided her; asked if disease was communicable	Frantic concern over Norman's return to college. Finally resigned to aiding in independence	Effort made to avoid helping him; pushed independence	Worried about ability to act as home nurses for son	Big psychological improvement; better spirits; more hopeful, ate better	At first parents were protective; Nancy was dependent. Peers forced her to be independent and she rebelled against parents
Greatest gain in improvement Self	No specific gain. Progress was day by day; never thought beyond one day	No specific period; perhaps in rehabilitation hospital learning first muscle power, then rehabilitation	No one period of great improvement; constant gain	Weaning from respirator	Progress in one month to ability to breath alone for 20 min.	Six months after leaving hospital; found she could do everything
Parents	Social readjustment 3 yr. post-polio	6 mo. in rehabilitation hospital	Constant gain	The last 6 mo. with 40 pound weight gain	Starting to walk after 2 yr.	Six months in rehabilitation hospital where she regained use of hands
Positive and negative incidents Self	*Pos.*—Starting back to school *Neg.*—Being snubbed by other people	*Pos.*—Small incidents indicating self-sufficiency: feeding, dressing self *Neg.*—Inconsideration of other people	*Pos.*—Traveling to Europe three years postpolio with friend *Neg.*—Realizing inability to walk	*Pos.*—Getting out of respirator *Neg.*—Left alone because sassy to nurse	*Pos.*—Getting out of respirator *Neg.*—Pneumonia following favorite nurse leaving	*Pos.*—Discharge from hospital *Neg.*—Feeling of never recovering while on visit home from hospital
Parents	*Pos.*—Graduation magna cum laude from college *Neg.*—Unfortunate love affair	*Pos.*—Norman's return to college *Neg.*—Prolonged period of paranoid delusions	*Pos.*—Trip to Europe *Neg.*—Realizing inability to walk	*Pos.*—Hiring psychiatrist to help with emotional problems. *Neg.*—Kenneth being ignored because rude to nurses	*Pos.*—Going to college *Neg.*—Being told Nicholas would never get off of rocking bed by famous doctor	*Pos.*—High scholastic achievement *Neg.*—Lack of consideration of parents by physicians at city hospital

Present physical status	Right foot drop; contractures of right hand muscles; generalized muscle wasting	No power in shoulder muscles; decreased power in left hand	Confined to wheelchair; wears girdle for abdominal support	Confined to bed for spinal fusion	Requires rocking bed for sleep. Only slight grasping movement of hands. Wears back and neck brace	No shoulder muscle power
Body image						
Self	Conscious of each muscle and function. Stress clothes, hair, face	Likes to have clothes which fit well. Not conscious of muscles in every day jobs, only when special skill required	Insistence upon immaculate dress. Likes swimming because of sense of coordination; well-being	Encased 12 mo. in body cast for spinal fusion. Fussy about fancy socks he is allowed to wear	Constant concern over ability to continue breathing. Interested in clothing details, e.g., ties	More conscious of standing up straight; minimizing deformity by dress
Parents	Frail body with beautiful face. Sally should emphasize assets	Frail young man unable to defend self physically	Meticulous in dress; emphasis on charming personality	Frail young man who is just beginning to gain weight	Frail instead of stocky robust boy of before; great interest in clothing now	Offset limitations present; emphasis on good grooming
Present personality						
Self	Heightened consciousness of self: mentally and physically. No basic personality change except increased interest in people	Basic personality unchanged: studious first-year law student. More interested in other's problems. Making an effort to establish heterosexual relationships	Personality unchanged. Delights in being center of attention, having other's pity, yet be independent. Interested now in helping others in worse condition	Afraid of hospital staff; feels they hate him. No drive to study while lying in bed, although one year of high school left	Not as interested in things but more in people now. Attention focused on details of environment. Making effort to establish heterosexual contacts	More serious, more understanding than peers. Appreciation of what I have when I see what others have. Attends college; works part time
Parents	Shy; feels physically unattractive, avoids heterosexual contact; lives to work; has anxiety attacks of inability to breath	Studious; minimizes physical disability; persistent in efforts to drive a car	Still opinionated, self-centered but more thoughtful. Realizes how much more he has than most and that he should be better	As mature as his peers or more than they are. Peers tell him their problems	Cheerful; rarely complains; determined to be as normal as possible; beginning to share mother's belief of complete recovery	More mature; very religious. Very aggressive, never gives up if she wants something. Refuses to date boys who mention polio

TABLE I.—CONT'D

TOPICS	SALLY O+	NORMAN O→	EDWARD O→	KENNETH O→	NICHOLAS O→	NANCY O+
Attitude toward disease and life goal Self	Would not trade the experience for anything; would not relive it for anything. Now has ability to take the pleasant and unpleasant. *Goal*—No longer to think of self as postpolio	Polio gives a maturing advantage. Do not try to hide physical disabilities, do not try to display it. *Goal*—Normal life with marriage	Polio gives certain amount of egotism. Polio victim should be integrated into life. *Goal*—To lead as normal a life as possible including marriage	No definite attitude about polio *Goal*—No plans until knowledge of future physical ability	The truth of limitations of the disease is dawning in stages *Goal*—To lead as independent a life as possible	Wishes polio had not happened to me; has made me more dependent upon God *Goal*—Marriage and normal family life
Parents	Polio has made parents more conscious of fellowmen. Both work for National Foundation	More conscious of fellowmen; more helpful. Mother works for National Foundation	Polio is rotten luck but must make the best of it. Polio makes a person feel more important than he is	Feel polio is terrible disease *Goal*—Too little known of potentiality; a problem of cultivating interests which can be admired by others. Both work for National Foundation	Polio was God's will and was done for a good reason. Nicholas will recover fully including neck muscles. Mother works for National Foundation	It is impossible to accept that there will not be complete recovery. Use electrotherapy for muscle stimulation. Both work for National Foundation

The patient and his family were frank in their discussion of the impact of poliomyelitis. Having been given the reassurance of anonymity, they were able to make statements such as follows: "One of the most serious weaknesses in polio therapy is the traditional distaste of the medical profession for the parents. A patient in a large hospital is like a cork on the ocean; nothing goes on for months except bobbing."

It was expected that each case study would be unique and that few similarities in reaction would be obtained. But after several interviews new patients and parents would remark that the questions indicated their problems were not unusual. Table I is included to demonstrate the similarities and dissimilarities of the cases. Although this series is too small to be statistically significant, yet it is interesting that common psychologic responses occurred in three to five of the six cases.

PREPOLIOMYELITIS PERSONALITY

When the prepolio personalities are compared, great variation is obvious; yet, with the exception of Kenneth, all were described as persistent in pursuing their goals. Kenneth has made the poorest psychologic recovery. On the basis of scholastic achievement, with the exception of Edward and Kenneth, this group is superior intellectually. Sally was valedictorian of her high school class; Nancy led her class; Norman was fourth in a class of 900; Nicholas was near the top of his private school class.

IMMEDIATE REACTION TO POLIOMYELITIS

Sally and Norman were described similarly by themselves and by their parents as excellent students, avid readers, and shy in heterosexual relationships. The most troublesome problem to both during the acute stage of bulbar poliomyelitis was their fear of mental deficiency. There appeared to be conclusive proof of this possibility. Sally noted that she was unable to understand the numbers on the door across the hall. She would try in vain to add or subtract one number from another. She was also unable to comprehend the meaning of words she read.

Norman found that he, too, could not understand the meaning of words. As soon as it was feasible, both youngsters returned to college where they worked to the point of exhaustion but attained high scholastic recognition to their own satisfaction. These two cases, particularly, indicate the need of early appraisal of the prepolio psychologic capacities. Thus, in the course of the disease, if areas of the body are deformed which have more emotional connotation for the individual, special consideration should be given to this area in the reassuring explanation of the physician. Perhaps even when involvement appears to be developing, the patient could be forewarned and reassured as to the ultimate outcome.

All the patients said they were often afraid to ask what was happening to them. In past reflection they realize that during the acute stage absurdly trivial incidents took on exaggerated significance and they too easily reflected and magnified the emotional tone of their environment. Yet, at the time, each incident was important and the more frequently it was treated as trivial by the others, the more likely the next incident

would be suppressed. They become afraid to ask questions.

Anxiety, fear, and terror have been frequently described as the immediate reactions to the onset of paralysis.[15, 22, 24, 26] Yet none of these patients recalled these reactions in the acute stage. Edward had recently seen the Sister Kenny movie and believed that with the Kenny technique everyone was cured. Norman's mother had had poliomyelitis at 6 years of age and had made a complete recovery. Kenneth and Nicholas thought of polio as the poster of the boy on crutches and considered polio as something which "hits your legs." None realized the extent of the disease for at least two to three weeks (Edward, Nicholas, Kenneth); yet, during this period each had been put in the respirator. Some, such as Sally, Nancy, and Norman, did not comprehend the muscle paralysis for five or six weeks. All described watching someone else move parts of his body during this period. Thus, it appears important to watch for symptoms of anxiety and fear for a period longer than is usually assumed. Sally said, "During the acute illness I had a peculiar inability to identify myself with my name. We didn't come together, my name and I. It was almost as though I should be rechristened." Noreen Linduska[18] in her book, *My Polio Past*, describes a similar feeling. "Something happened and I became a stranger. I was a greater stranger to myself than to anyone. . . . I suddenly had the very confusing mental and emotional conflict of a lady leading a double life."

Fortunately, during the period of most acute pain, the mental unawareness shielded the mind from the realization of the extensive involvement. This mental unawareness has been described by Ripley and associates[22] as part of Sister Kenny's concept of "mental alienation." Yet, as each understood what had occurred, each became terribly frightened at every shift of his body upon which he could no longer depend and which seemed so completely dissociated from himself. Physically, each had reverted to an infantile state and of necessity had to be treated as an infant whose helplessness demands care. Emotionally, the patients reacted like infants who sense their parents' anxiety and utilize it for their own satisfaction. They became petulant, demanding, easily upset emotionally, and irritable.

Since they could no longer depend upon themselves they turned to their environment for sources of gratification and, with the exception of Kenneth, all turned to religion. Neither of the two Jewish adolescents, Sally or Norman, had grown up attending the synagogue regularly, yet both reacted to the illness in the traditional Hebrew manner, which regards illness and physical disability as sinful. The Jew is being punished and is atoning for his wrong-doings. Sally thought that the method of atonement was to be as good as possible, even to the woman who scrubbed the floor. Norman felt that he must atone for his masturbation, which had caused his poliomyelitis, and begged forgiveness from the rabbi. Sally's parents also turned to the Hebrew traditions for saving the dying: visiting the graves of their ancestors and carrying the scroll of the synagogue. The two Catholic adolescents, Nancy and

Nicholas, reflected the church's attitude of sickness and disability as a way to grace. They were encouraged in this type of prayer by priests, family, and friends, who felt the disease was God's will and brought upon them for a good reason. Edward, who is a Protestant, relied most upon his own inner strength and prayed for this strength. This attitude is apparent in a dream he had when he was afraid of dying; he was brought before the judgment seat to argue why he should live.

As opposed to their children's mental unawareness of the events occurring, the parents from the beginning were terrified, anxious, felt helpless, but none expressed hopelessness. Although they could observe the paralysis, the wasting muscles, and the prominent bones, they were certain that their child would recover completely. In the rehabilitation hospital they were exposed to other patients who had been ill several years previously and had many obvious handicaps, yet they refused to believe that their child would not recover. With the exception of Norman's parents, all recalled periods of severe depression following a physician's demonstration of a person who was severely handicapped yet could care for himself. The physicians undoubtedly thought they were injecting a note of optimism if the parents felt the child would never recover, or introducing reality if the parents appeared to expect too much recovery. It is probably fortunate that none accepted the limitations placed by physicians. Although the parents' determination and the amount of recovery may not be related as cause and effect, every child has recovered more function than the physicians had estimated.

REHABILITATION

The process of rehabilitation is agonizingly slow as voiced by all patients and parents. And it is a process which can never be said to be completed, for all the patients, with the exception of Sally, are still seen by the physiotherapist one to five times each week. After eight years Sally refused any more physiotherapy against the strong protest of her parents.

Only Kenneth hates physiotherapists and is afraid they may injure his muscles. He has had more than ten physiotherapists over a three-year period. In every other instance the physiotherapist was mentioned by the patient as the most important person in rehabilitation. The relationship can aptly be compared with that between infant and mother. The age and sex of the therapists were unimportant. It was the characteristics which they had in common with an ideal mother which was important. The qualities ascribed to the therapist are an attitude conveying physical security, a guiding yet unauthoritarian hand, a faith in potentialities, and an expectation of future gains. Sally, Edward, Norman, and Nicholas mentioned watching with wonder as the therapist passively manipulated each limb through movements of which he was voluntarily incapable. Their dependence was expressed: "She was my ability to move, giving me strength to move myself . . . she took my leg and moved it." "Her faith in me was the key to success." "He was for me if I worked and promised slow constant gain." "He im-

pressed upon me the importance of concentrating upon each muscle." The emotional response to this encouragement was amazingly similar to the response of the young child to the mother's demands. An infant will give up the demand of immediate satisfaction of his desires in return for his mother's love. So, also, on the foundation of such a relationship the polio patient, who of necessity had his demands satisfied and thus developed selfish attitudes, sooner or later sacrificed his own pleasure because of his relationship with the physiotherapist. The motivation of doing something for someone whom he loves is indicated in statements: "The first day I tried to stand beside my bed and fell to the floor I felt that I had failed her." "We spent nine months learning to get into a wheelchair . . . if I failed it was not so much a failure but if I succeeded I felt an accomplishment." "Each day he asked what muscle I could move; when I showed him we rejoiced together." The difference between the attitudes of the physicians and physiotherapists was striking. Of course, there were exceptions to this statement, but most of the physicians told the patients and their parents to resign to life in a wheelchair or on crutches. A definite limit was set upon the amount of possible recovery, whereas the physiotherapists "accentuated the positive and eliminated the negative."

THE PARENTS

The quality of the patient-therapist relationship naturally encroached upon the child-parent relationship. During the school years the parents had come to accept that other adults were important in the life of their child. But during the acute illness, with the regression physically and emotionally on the part of the child, the parents, too, reverted in emotional response. They felt useless when the physiotherapist took over the re-education of body and spirit. With the exception of Edward's stepmother, all the parents reacted by hovering over the child, trying to shield him from daily physical and emotional contacts with the world. Edward's stepmother remarked, "It is rotten luck, but we must make the best of it. The minute you say 'you poor boy' he only pities himself." Because of their economic position only one set of parents, Sally's, succeeded in this attempt to protect their child from the world. Today Sally states, "One of the biggest mistakes of rehabilitation was the isolation from day-to-day contacts." The past two years have been the period of most difficult emotional adjustment for this girl, who is now trying to live a life outside the family cocoon. In their uncertainty of what to do now, her parents use the medical profession as a scapegoat and feel that it is "the inadequacy of medicine" for no one to have mentioned the social effect of polio and to have tried to assist her.

Nancy's parents overcame the threat of losing their child by actively allying themselves with the therapist. Her father took a course in physiotherapy in order to give muscle exercises under the therapist's direction. Since this man also has extensive electrical knowledge, he built a machine to stimulate the muscles. Watching the muscles contract by application of electric current gives these parents constant hope. On the other hand,

Kenneth's father has replaced the therapist. Kenneth teaches his father what the therapist does and then allows him to do more than he allows the therapist, of whom he is afraid.

All the parents realized that their child must be pushed if he is not to lapse into an attitude of discouragement, depression, and dependence. The patients also realized the need for this type of support, but they resisted consciously and unconsciously the efforts to push them out of the attitude of self-pity. Yet the pushing was a silent indication of belief in potential ability, which was a necessary foundation for self-reliance. Finally each was able to take over for himself. This is best expressed by such remarks: "I made up my mind to get out of the respirator . . . to walk . . . to feed myself." The parents find it difficult even now to keep from reaching out a hand to help their child put on a coat or get out of a chair, but wisely they refrain. Kenneth's parents do not share this approach and make no effort to help him to be independent. They feel that they are at the mercy of the physicians' decisions, and that they must prepare themselves for a life of nursing centered around a bed and wheel chair. Recently Kenneth has come to appreciate the effect of this attitude and is greatly disturbed as to how to free himself from his ties made more binding by present hospitalization.

PRESENT ATTITUDE TOWARD POLIOMYELITIS

From answers to questions concerning positive and negative incidents and the period of greatest gain in improvement, only general conclusions can be reached. Important incidents were related to the goal of gaining self-sufficiency and feeling like everyone else. The desire to be treated no differently from anyone else is vehemently expressed as a desire not to associate with other postpolio people. Sally refused to date two men who had had poliomyelitis. Nancy will never date a fellow again if he mentions that she had polio. Edward refused to associate socially with "postpolios"; although it becomes obvious upon talking with him that his refusal is based upon his desire to be the center of attention which a wheelchair grants him and which is maintained by his witty and charming manner. Only Norman made his first social contact by dating a girl who had had polio but had fewer residua. As he felt more socially secure he has dated other girls instead. The parents, on the other hand, with the exception of Edward's stepmother, are active in the National Foundation for Infantile Paralysis.

A desire for social acceptance and for a personal feeling of body normalcy has altered the body image of these young people. The term "body image" is used by Dr. Paul Schilder[14] to denote the picture each person has of himself and his body. When disease occurs, the body image must take on a new alignment. The deformed part must fit into the image of self. The patients understand their limitations, yet they try to draw attention away from the affected area. Sally, Norman, and Nancy constantly practice each pattern of movements necessary for accomplishing an act in an effort to make it appear as normal as possible. Edward likes swimming because it gives him a "sense of coordination and well-be-

ing." All have become fastidious in their personal grooming. The young women emphasize their pretty faces and hair; the men, their suits and ties.

Again, with the exception of Kenneth, all the patients have actively reentered life. Their expression of life goals—to be a lawyer, a teacher, an investor, a social researcher, and for marriage—reflected their implicit desire for as normal a life as possible. And it is explicit in the hope of all: "no longer to think of myself as a postpolio." It may be argued that this is impossible since each of these people had marked physical incapacities; therefore, why not help them to realize this fact? Kenneth and his parents are the only ones in this group who have succumbed to this attitude and they have abandoned hope.

The patients and families have learned that it is they who must be aggressive socially. As a whole, society reacts to a disability to the detriment of the rehabilitation of the disabled. Those who deal with the disabled person react on a personal conscious and unconscious level. Because of their own mixed emotions they find that avoiding a disabled person is the easiest method of handling the situation. Fortunately for these "postpolios," the slow recovery and constant contact with many people heightened their interest in other people. They and their families feel that polio has matured them beyond their years. They are able to take "the unpleasant with the pleasant," as Sally expressed it. Nancy feels more serious than her peers, appreciating more fully what she has when she sees what others have. Norman describes polio as giving a "maturing advantage." Edward calls it "a certain amount of egotism" that develops as a result of being able to overcome the disabilities of the disease. Nicholas had found that he can reach out toward others from his wheelchair by his interest in each as an individual.

DISCUSSION

At present, there is no known medical method which will test the ultimate outcome in the rehabilitation of these young people. Morris Grayson's[14] concept of acceptance might be applied in an effort to evaluate the degree of rehabilitation. His term acceptance includes physical, social, and psychologic rehabilitation. Physically, the patient should be aware of the nature of his disability, its origins, complications and prognosis. Socially, the patient should be realistic toward his job, housing, family, and other relations. Psychologically, the patient should have no serious emotional symptoms referable to the disability.

All of these patients and their parents have accepted the nature of the disability, its origin, and complications. But, with the exception of one patient, they have not accepted the prognosis. The parents are convinced that their child will recover completely. The role of the physician in such a situation is difficult. When the child is in the respirator he may try to encourage the parents by showing them another child who is handicapped but can care for himself. Here the parents' reaction was one of depression. One parent expressed the attitude of all parents when he said. "I am looking for perfection." Although the exact nature of the deformity may have been described by

the physician, the inability to understand did not depend upon the intellectual status of the patient or parents. One family knew what they wanted to believe; hence, they have gone from physician to physician, professing ignorance as to the meaning of the disability. A physician may encourage the patient and parents to strive for complete recovery. This has been done in three of these cases. But then the problem arises as to whether this placed too great a burden upon the patient.

It seems natural that, although the therapist takes over the parents' position, the parents should feel most closely allied with the physiotherapist who emphasizes slow constant gain. The patient has to choose between the physician's prognosis which seems negative and the parents' and the therapist's favorable prognosis. The patients have chosen the favorable prognosis and have remained strongly attached to the physiotherapist who continues to give therapy. Since the therapist establishes an intimate relationship with the patient and parents, it would seem wise for the physician to work closely with the therapist. Through the therapist the physician could direct the acceptance of a body image with a deformity. And perhaps the physician would learn when it is important to be optimistic without feeling that with this attitude he will only fall short of his goal.

It has been indicated that society is disoriented with regard to the "postpolio." He has to integrate himself into society. In their jobs and family life these patients have found acceptance. But their avoidance of other people who have had poliomyelitis or those people who mention poliomyelitis indicates that postpolio clubs or group therapy would not be successful with this age group.

During the acute stage of poliomyelitis these patients developed a mental unawareness of the paralysis. Anxiety, fear, and terror became manifest two to six weeks after the onset of the paralysis. Therefore, the physician should be aware that the onset of these symptoms may be later than is generally expected. And if areas of the body are deformed which have more emotional connotation for the individual, the patient should be forewarned as to the ultimate outcome.

Only one of these patients has severe emotional symptoms referable to his disability. He is a young man who has been hampered in his acceptance of physical and social rehabilitation. The emotional symptoms have appeared only where there is conflict or uncertainty in the physical and social aspects of rehabilitation.

Thus, even three to eight years after the acute stage of poliomyelitis, these young men and women have not fully accepted their disability. These facts seem to indicate the importance of a long-term individual program with the patients and their parents. Rehabilitation of parents is as essential as that of the patients. In this study the parents also reverted in their emotional response to the child who had again become their helpless infant.

Interviewing the parents not only revealed their problems in the rehabilitation of their child, but it also had psychotherapeutic implications.

Parents asked whether others had similar problems and appeared relieved to hear that they had. They all mentioned that this was the first time they had been asked to express their feelings. This study indicates the value of rehabilitation of parents as well as patients.

SUMMARY

1. Those patients whose prepoliomyelitis personality was described as "persistent in pursuing their goals" have made the best recovery.

2. During the acute stage of poliomyelitis, trivial incidents took on exaggerated significance. If these incidents were ignored by physicians, nurses, or parents, the poliomyelitis victim became afraid to ask questions.

3. The reactions of anxiety, fear, and terror appeared two to six weeks after the onset of paralysis.

4. Patients and parents reacted to the illness in a manner appropriate to their cultural background.

5. The parents felt useless when the physiotherapist took over his task, since they had reverted emotionally to being parents of a helpless infant.

6. In general, the physicians set a definite limit upon the amount of possible recovery; the physiotherapists emphasized slow constant gain.

7. The parents refuse to believe that their child will not recover completely; therefore, five of these patients continue to receive physiotherapy three to eight years postpoliomyelitis.

8. The patients avoid association with other postpoliomyelitis people. They desire social acceptance and a personal feeling of body normaley.

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Comments on Current Literature

HEMORRHAGIC FEVER*

THE clinical entity now designated as hemorrhagic fever was first brought to the attention of the Western World by the occurrence in 1951 of a new and strange disease among the United Nations forces in Korea.[1, 2] The 1951 outbreak was limited to a comparatively small geographic area in Korea. The distinct seasonal incidence of the disease was apparent at that time, with the greatest number of cases appearing in the late spring and early summer, continuing into fall. By December the incidence had declined, and the disease remained quiescent until the following spring (1952), when a second outbreak occurred: 500 cases between mid-April and mid-July.[3] Extensive studies were initiated in an attempt to understand the new disease entity and to control its spread among the United Nations forces.

While the results of many of these studies are unpublished as yet, reports have been appearing from time to time. In April, 1953, George M. Powell[4] published a preliminary summary of clinical manifestations and laboratory studies based on fifty-five cases, findings which had been presented at a symposium on the disease held in Tokyo, Japan, in December, 1951.[1, 2] The May, 1954, issue of *Medicine* carries an extensive final report by Colonel Powell[4] based on a study of 300 of the cases seen in 1951. Among this group of 300 patients, nine deaths were recorded. Since the Osaka Army Hospital, Osaka, Japan, served as a center for the treatment of hemorrhagic fever, opportunity was afforded for the accumulation of significant information. Careful medical records were possible, and an attempt was made to obtain detailed histories. From these records the author and his associates were able to define a common pattern of clinical manifestations consisting of three stages: the invasion, the toxic, and the convalescent stages.

1. The invasion stage was characterized by high fever, the main symptoms and signs being those commonly associated with acute febrile illness. Laboratory studies at this stage usually gave values within normal limits.

2. Initially the toxic stage presented symptoms and signs of shock, later of renal failure, accompanied by evidences of hemorrhagic diathesis. Cerebral toxicity and gastrointestinal dysfunction were apparent throughout this entire period. Significant laboratory findings were albuminuria, oliguria and hyposthenuria; azotemia with hyperpotassemia; leukocytosis with leukemoid reaction and atypical lymphocytes; hemoconcentration and rapid sedimentation rate; thrombocytopenia; prolonged bleeding time and increased capillary fragility.

3. The convalescent stage of the disease was characterized by the symptoms and signs generally present during recovery from severe illness. Polyuria was the most marked and persistent finding. With the exception of rapid sedimentation rate and hyposthenuria which required in some instances as long as twelve to sixteen weeks, laboratory findings returned to normal limits during early convalescence. Phenolsulfonphthalein excretion was below normal for as long as fourteen weeks; except in rare instances, the power of urine concentration had returned by the sixteenth week.

Chills constituted a striking feature of the early invasion phase, occurring in 90 per cent of the cases. Severe headache was a marked manifestation

*Hemorrhagic fever, described clinically in Northern Manchuria as early as 1935, has had various names: Manchurian fever, Songo fever from the Songo district in which it occurred, Nidoko disease, Kokka disease, Korin fever, etc.

in 85 per cent, and backache in 78 per cent. As is seen from the author's summary, severe manifestations increased during the second phase of the disease, evidence of hemorrhagic diathesis and renal involvement being particularly apparent. Urine was often dark brown in color, smoky in appearance, and red, or grossly bloody, and elevation of nonprotein nitrogen level was associated with the renal involvement.

The convalescent stage began, as a rule, about the tenth to the fourteenth day of illness with termination of the oliguric phase and onset of polyuria. In most instances recovery was slow, and the period of illness lasting from six weeks to four months; in general, however, recovery appeared to be complete with no residuals and without recurrence. The nine deaths in this series of 300 patients occurred on the fifth to the seventeenth day of illness.

In Powell's report the pathology of hemorrhagic fever is described in considerable detail and is well illustrated by pertinent photomicrographs. The most impressive pathologic findings were in the kidneys, the cortex appearing pale and swollen, and the medulla congested and hemorrhagic. This unusual and characteristic pathologic finding is illustrated by photographs of a gross specimen showing the striking features of the renal involvement occurring in this disease. Important microscopic findings included widespread vascular dilatation and engorgement with hemorrhage in the kidney, heart, pituitary, adrenal and gastrointestinal tract. Widespread damage to arterioles and capillaries accounts apparently for many of the physiologic abnormalities observed in this unusual disease entity.

The observation of a leukemoid response during the toxic phase, with a preponderance of immature cells in the granulocytic series associated with atypical lymphocytes, is of considerable interest. Platelets during this stage of the disease were relatively few in number and appeared larger than normal.

Certain epidemiologic features of the disease are interesting: the rather restricted geographic distribution, definite seasonal incidence, and possible association with insects and vermin. In this particular study, 61 per cent of the personnel becoming ill with the disease reported that they had slept on, or close to, the ground, and 21 per cent reported shelter mates with a similar illness. The presence of rats and mice was noted; ants were numerous; however, the incidence of fleas, lice, mites, chiggers, etc., was not considered unusual.

Studies of the epidemiology of hemorrhagic fever have been reported recently by various groups comprising the Epidemic Hemorrhagic Fever Field Unit: Gauld and Craig, January, 1954; Traub, Hertig, Lawrence, and Harris, May, 1954, both reports appearing in the *American Journal of Hygiene*.[5] According to these reports, person-to-person transmission does not occur; food and water supplies do not seem to be involved, but the distribution of human cases does seem to follow that of arthropod vector and rodent reservoir. Traub and his associates (May issue, 1954) conclude that "trombiculid mites (chiggers), laelaptid mites, fleas, and ticks may all be regarded as potential vectors, but that chiggers alone can be correlated with the epidemiology of the disease." "Potential reservoirs are more likely to be found among certain field rodents or other mammals rather than among domestic rats and mice."

Despite exhaustive studies, the American investigators have not been able to come to any conclusion as to the nature of the etiological factor involved in hemorrhagic fever. Japanese and Russian workers, however, report the isolation and filtration of a virus from the blood and viscera of hemorrhagic fever patients. Russian workers succeeded apparently in producing the disease in human volunteers by the intravenous administration of defibrinated blood, and by the intramuscular inoculation of urine from patients ill with the naturally

occurring disease. Japanese investigators claimed to have produced the disease in monkeys by injections of a suspension of triturated mites removed from field rodents in endemic areas. Both Japanese and Russian workers tend to incriminate the vole and the striped field mouse as reservoirs in nature, with the general conclusion that transmission to man occurs by arthropod vector. Further studies along this line would be of interest and importance.

Awareness of exotic, unfamiliar illnesses in distant countries is sometimes of academic interest only, or becomes important only when unusual circumstances permit travel to areas of the world where these disease-producing agents are endemic. However, in this day of widespread interchange of personnel among nations, for whatever reason, these diseases assume a new importance. It is of interest that in the May, 1954, issue of the *Annals of Internal Medicine*, Hibbard, Ballard, and Gibson[6] of Kansas City, Missouri, report a case of hemorrhagic fever: "A Case of Epidemic Hemorrhagic Fever in the United States." In this case presentation, the authors describe the typical course of epidemic hemorrhagic fever occurring in a 26-year-old Korean veteran who had left the endemic area at least three weeks prior to onset of illness. The detailed history, physical findings, clinical course, and laboratory studies support the diagnosis of hemorrhagic fever. Noteworthy among the hematologic findings in this patient was the bizarre leukemoid blood picture observed.

The rapid return of travelers and personnel from such areas of the world made possible by present-day transportation facilities emphasizes the importance of recognizing hitherto unfamiliar clinical syndromes.

RUSSELL J. BLATTNER.

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News and Notes

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The following are schedules for the coming oral examinations to be held by the Board:

Chicago, Ill., Oct. 8, 9, and 10, 1954.
New Haven, Conn., Dec. 3, 4, and 5, 1954.

The eighth annual meeting of the **American Academy for Cerebral Palsy** will be held on Nov. 4, 5, and 6, 1954, in Williamsburg, Virginia, at the Williamsburg Inn.

The **National Foundation for Infantile Paralysis** has announced the award of grants and appropriations totaling $2,486,244, effective July 1, for research and professional education in poliomyelitis and related fields. Grants went to thirty different medical schools, universities, hospitals, research institutions, and educational organizations in the United States and two in other countries. Of the total sums authorized, $1,506,148 was granted for research in virology and epidemiology and in prevention and treatment of aftereffects of poliomyelitis and related conditions, and $980,096 in grants and appropriations was allocated for programs of professional education.

The **University of Pennsylvania Graduate School of Medicine** announces two courses in Pediatric Hematology for practitioners, Sept. 13 to 15 and 16 to 17, 1954. I. "Practical Pediatric Hematology" will be given Sept. 13 to 15, under the direction of Dr. Irving J. Wolman, Associate Professor of Pediatrics and Director of Laboratories of The Children's Hospital. Dr. Wolman will be assisted by Drs. Benjamin Dickstein, Paul G. Eglick, Timothy Talbot, George Ward and others. II. "Rh and Other Blood Group Incompatibilities in Relation to Erythroblastosis Fetalis" will be given on Sept. 16 and 17 under the direction of Dr. Neva M. Abelson, Assistant Professor of Pediatrics and Director of the Philadelphia Serum Exchange Division of The Children's Hospital. These courses will be given at The Children's Hospital of Philadelphia and will run from 9:30 A.M. to 4:30 P.M. daily. For information as to fees and application forms, address: The Dean, Graduate School of Medicine, 230 Medical Laboratories, University of Pennsylvania, Philadelphia 4, Pennsylvania.

A course in practical *electrocardiology* will be presented during the week of Dec. 6 to 10, 1954, under the auspices of **University of Texas Postgraduate School of Medicine, Baylor University College of Medicine,** and the **Houston Heart Association.** The guest lecturer will be Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiology of the National Institute of Cardiology of Mexico City. The course includes adult and pediatric electrocardiology. For further inquiry and advance registration, address The University of Texas Postgraduate School of Medicine.

A number of *fellowships* for the academic year 1954-1955 will be available for research workers who may wish to work at the Laboratories of the **International Children's Centre,** Paris. At present the program of research of the Centre is essentially connected with problems of antituberculosis vaccination and antipertussis immunization. The grants amount to 60,000 French francs per month. Traveling expenses from their residence to Paris will have to be borne by the research fellows. Research workers who wish to apply for a fellowship are requested to send their application together with their curriculum vitae, record of previous work and testimonials of their chiefs of service to Professor Bugnard, International Children's Centre, Château de Longchamp, Paris 16°.

Book Reviews

The Emotional Problems of Children. A Guide for Parents. Harry Joseph, M.D., and Gordon Zern, New York, 1954, Crown Publishers, Inc., 310 pages. Price $3.75.

A recent addition to the numerous books on the same or similar subjects which have been written and published in recent years. The senior author is director of the Guidance Center at New Rochelle. The writers have been influenced in their interpretation of child behavior by the Freudian school, but the text is unusually free of psychiatric jargon.

Fundamentals of Otolaryngology. Second edition. Lawrence R. Boies, M.D., Philadelphia, 1954, W. B. Saunders Company, 487 pages. Price $7.00.

This book by the professor of otolaryngology at the University of Minnesota is essentially a text for undergraduate teaching rather than for the specialist. A number of Dr. Boies' associates have contributed chapters. "Modern Medication," which has so changed the entire practice of otolaryngology in recent years, is the subject of a separate chapter.

Human Development. J. P. Zubek and P. A. Solberg, New York, 1954, McGraw-Hill Book Company, Inc., 476 pages. Price $6.50.

This text covers the entire age span. Although most studies of development have been made on cross sections, the authors have used a longitudinal approach in the presentation of the material. Thus the various subjects considered, such as learning, emotional development, intellectual development, etc., start with the earliest periods and are carried on through the later periods of the life cycle as childhood, maturity, and old age. The text is unusually clear and well written. There is a lot of information in the book that is of interest to physicians as well as to those concerned purely with psychology.

Fundamentals of Neuropathology. William B. Dublin, M.D., Springfield, Ill., 1954, Charles C Thomas, Publisher, 685 pages. Price $18.50.

A text on neuropathology by the associate professor of pathology at the University of Colorado and chief of the laboratory service of the Veterans Administration Hospital. The text is chiefly of interest to pathologists. It is well illustrated and well presented. The chapters on congenital deformities and inflammation are the parts of particular interest to the pediatrician.

Pediatric Problems in Clinical Practice. Edited by H. Michal-Smith, Ph.D., New York, 1954, Grune & Stratton, 310 pages.

Thirteen specific clinical problems are discussed by authors well known for work in specific fields, as, for example, "The Emotionally Disturbed Child" by Hulse, "The Schizophrenic Child" by Bender, "The Allergic Child" by Ratner, "The Diabetic Child," by Priscilla White, and the "Epileptic Child" by Lennox. Some of the discussions are more slanted to the general public than to the medical reader. While as a whole the discussions are good, there is a decided unevenness. The editor presents the chapter on "The Mentally Retarded Child." The reviewer was puzzled in this chapter as to why a detailed three-page outline in small type of a physical examination is included. It might fit into a text on physical examination for second-year medical students, but in a text of this type it is decidedly out of place. It almost discouraged the reading of the remainder of the chapter. However, we found this a sound general discussion of the problems created by a mentally retarded child. The discussion of diabetes and of epilepsy are the two best chapters in the text in the opinion of the reviewer.

The Jealous Child. Edward Podolsky, M.D., New York, 1954, Philosophical Library, 147 pages. Price $3.75.

A popular discussion of the causes of the emotion jealousy in a child. The author considers the various physical conditions such as obesity, chronic invalidism, speech disorders, etc., and the environmental causes such as sibling rivalry, illegitimacy, neglect, and the unwanted child.

Auditory Disorders in Children. H. R. Myklebust, New York, 1954, Grune & Stratton, 367 pages. Price $6.00.

The subtitle for this text by the professor of audiology at Northwestern University is "a manual for differential diagnosis," and it is chiefly designed for the audiologist and pediatrician. The author divides auditory disorders into four groups: due to peripheral deafness, due to aphasia, due to psychic deafness, and due to mental deficiency. After a discussion of each group the author follows with a discussion of examination methods and procedures which includes auditory tests and the psychologic examination. Following comes a chapter containing illustrative cases, and finally, a discussion of recommendations for training in each of the four types of auditory disorders.

The material upon which the study is based is the author's well-known work in the Hearing and Aphasia Clinic of Northwestern University at Evanston. The necessity for cooperation of the various disciplines—audiology, pediatrics, psychology, education, etc.—is stressed, as is the strategic position of the pediatrician as he is often the first to encounter the child with an auditory disorder. The text is well suited to give the pediatrician a good background in meeting the problems of deafness as he encounters them in his practice. If recognized early and accurately diagnosed as to cause, much can be done for the deaf child.

Modern Problems in Pediatrics. Edited by A. Hottinger and F. Hauser, Basel, 1954, S. Karger, 816 pages. Price Swiss francs 60.

This volume, which the editors express the hope will be the first of a series, is dedicated to Prof. Ernst Freudenberg, of Basel, on the occasion of his 70th birthday. In all, some eighty scientists from many countries were invited to contribute. The prefatory part contains a tribute to Prof. Freudenberg by Paul György and a bibliography of Freudenberg's publications. The editors have not simply asked a large number to contribute in honor of Prof. Freudenberg, but have attempted to cover the development and problems of various special pediatric fields. Thus the material is arranged in fifteen main divisions with from two to several articles in each field. The selection is excellent. With so many contributors the individual discussions are necessarily rather brief. Among a number of American contributions are those of Warkany, "Prenatal Diseases"; Cl. A. Smith, "Perinatal Mortality as a Field for Pediatric Activity"; Gordon, "Retrolental Fibroplasia"; Darrow, "Parenteral Fluid Therapy"; L. Wilkins, "Treatment of Virilizing Adrenal Hyperplasia With Cortisone"; A. B. Sabin, "Avirulent Viruses for Immunization Against Poliomyelitis." The text is filled with well-known pediatric names from other countries, such as Fanconi, Wallgren, L. F. Meyer, Debré, and Keller.

The original communications are in English, German, or French. Each, however, is followed by an excellent summary in the two other languages. It is an excellent and interesting collection which reflects the widespread and varying interests of pediatrics throughout the world, and the many problems which scientists are trying to solve.

Editor's Column

THE NEW YORK CITY REHABILITATION PROGRAM FOR CONGENITAL HEART DISEASE

THE report on the rehabilitation program for congenital heart disease of the New York City Department of Health on page 273 of this issue discusses a number of matters that are of interest. First of all, the assuming by the municipality from tax funds the cost of hospital treatment and care outside of public institutions. The criteria for acceptance of a hospital to the program are based on standards set up by an Advisory Committee appointed on the recommendations of the New York Heart Association. It is a splendid example of the relationships that should exist everywhere between public and private health agencies. Unfortunately there is often competition between the two and a jealousy of "rights" among the executives. Whether a similar arrangement exists in other communities we have no means of knowing. With the steadily increasing cost of medical care, and private hospital deficits, the program serves as an example of a trend in medical economics which might well be the pattern of future developments.

Aside from the economic implication of the program, the analysis of the New York experience of the congenital heart program brings out a number of findings of strictly medical importance. Perhaps the most striking of these is found in Table V, Changes in Diagnosis. In forty-six of 129 cases in the program (36 per cent) a change in the diagnosis was made after the diagnostic work-up. Further, in five of sixty-nine patients operated upon (7 per cent) the diagnosis was again changed, three times at autopsy and twice obviously at the time of operation. In ten nonsurgical cases which came to autopsy the diagnosis made in the work-up was wrong in seven and correct in only three. Despite the remarkable progress that has been made in recent years in the diagnosis of the specific lesion by fluoroscopy, the electrocardiogram, cardiac catheterization, and angiocardiography, it is apparent that there is still a tremendous opportunity for the cardiologist working in the field of congenital lesions, both as to the refinement and interpretation of old measures, as well as the development of new diagnostic aids.

The great strides that have been made in recent years are well shown in the figures for results in Table III. In sixty-nine of the 129 patients in the program it was thought that an operation might help. In forty-nine of these sixty-nine (70 per cent) there was a cure (23 per cent) or definite improvement. The surgical mortality was only twelve, or 17 per cent.

SAMUEL J. CRUMBINE

THE death of Dr. Samuel J. Crumbine in July, at the age of 91, marks the passing of another of a group of men who, while not classified as pediatricians, made important contributions to the development of pediatrics. Among others in this group were such men as William H. Park and Sir Arthur Newsholme. Crumbine was a most unusual character, small in stature and quiet and modest in action. However, he was a lion in courage, who led by persuasion rather than by domination. His early medical years, beginning in 1885, were spent in practice in the frontier town of Dodge City, Kansas, famed for its "outlaws." Some five years ago he described his medical adventures in these days in an interesting book of reminiscences, *Frontier Doctor*.

In 1904 he became executive director of the Kansas State Board of Health, where he gained national recognition as a health officer. While popularly known for his "swat the fly" slogan, and his successful campaign to outlaw the common drinking cup and roller towel from railway trains and public places, to the pediatric group he was famed for his pioneer efforts for pure milk and dairy inspection, and for his campaign for immunization against diphtheria with the toxin-antitoxin mixture which had been developed by Dr. Park. Dr. Crumbine always worked for and through the practicing physician, and inaugurated the plan, later adopted in many states, for a visiting pediatrician to travel from community to community, holding clinics where the local physicians for miles around brought in their puzzling pediatric cases. The clinic was followed by a get-together dinner and a lecture.

In 1923 he was persuaded to desert his native state and become executive director of the American Child Health Association, a position he held until 1936 when the association was disbanded and Dr. Crumbine retired from active work. He gave the association a much-needed strong staff leadership, not only through his wisdom and clear thinking, but through the respect in which he was held by workers in the field of child health throughout the country. One of his outstanding accomplishments during this period was a survey of the child health conditions in Puerto Rico made at the request of President Hoover. His report and recommendations led to the establishment of a six-year plan for the relief and rehabilitation of children in that country which was under the aegis of the United States.

We are quite sure that most of the pediatricians of today have never heard the name of Samuel Crumbine, for nearly all who knew him well and were associated with him in his work for better health for the children of America are no longer living. It is for this reason the JOURNAL pays its respect to a man who was a pioneer worker and accomplished much in the field of child health.

"LETTERS TO MY DAUGHTER"*

A SHORT time ago the JOURNAL received a review copy of a small book entitled *Letters to My Daughter*. Because of the title and its being sent to a pediatric journal, the editor expected to find a text on health advice for girls written in the form of letters. Much to his surprise it turned out to be one of the most delightful and well-written collections of short essays on various topics we have seen in years, and it has been a long time since we have enjoyed a book so much. It is filled with wisdom. The author, Dagobert D. Runes, is an Austrian philosopher, and of an earlier book, *Letters to My Son*, Albert Schweitzer commented, ". . . we both walk the same path."

It is hardly a book for technical review in a specialized medical journal, but the editor feels he will do a favor to JOURNAL readers by calling their attention to the volume. There is one "letter" which contains such a gem of devastating criticism on a medical topic that, with the kind permission of the publishers, we quote several paragraphs:

"There has been a strong tendency in our century to picture the parent as some sort of inhibiting malefactor in the development of an otherwise perfectly adjusted young person. One of the most effective propagandists of this notion was a Viennese physician obsessed with the idea that every movement, talent, wish and aspiration in man and woman is caused by some inhibited sexual craving.

"When I was still a high school boy in Vienna I took my best girl to one of his lectures. I was very fond of the girl and we used to sit for hours on a bench at the Danube Canal watching the little boats go by and dreaming of the world of tomorrow—our world, of course.

"My girl listened to Dr. Freud with his incessant and repetitious references to male and female sex organs, normal and abnormal sexual activities, and after a while she said, 'Let's leave him, he is just a dirty old man.' And we went back to our bench, holding hands and dreaming of the world of tomorrow—our world, of course.

"I don't think that listening to Freud's muddled and muddy lectures and hunting for his sex symbols behind every door knob and every pocketbook has done anyone any good, except perhaps a few thousand licensed and unlicensed practitioners who take careful notes of what couch-ridden, half-hysterical and half-posing middle-aged women and elderly men enjoy relating as alleged occurrences in their respective baby lives.

"I have often wondered what these psychoanalysts do with their notes after they have finished with them. It takes anywhere from two to five years to put down the notes, and either the so-called patients, who certainly justify the name, have led terrific and extremely long sex lives in their infancy, or they just love to talk about it in the Freudian vernacular, which to some people seems a source of gratification in itself.

"I have never in my life met a person, man or woman, who was cured by psychoanalysis, if he ever had an ailment to begin with. But I have met a lot of people who, under analysis, seemed more utterly confused than before. I am almost inclined to say that as time went on they suffered more and more from progressive psychoanalysis. But I presume that so long as there is money in it there will be practitioners, and there also will be those of whom there is one born every minute."

*_Letters to My Daughter_. Dagobert D. Runes, New York, 1954, Philosophical Library. Price $2.50.